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(54) Title: NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF CERVICAL CANCER

(57) Abstract: The invention relates to newly discovered nucleic acid molecules and proteins associated with cervical cancer including pre-malignant conditions such as dysplasia. Compositions, kits, and methods for detecting, characterizing, preventing, and treating human cervical cancers are provided.

WO 02/101075 PCT/US02/18638

NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF CERVICAL CANCER

- 1 -

5 RELATED APPLICATIONS

The present application claims priority to U.S. provisional patent application serial no. 60/298,159, filed on June 13, 2001, U.S. provisional patent application serial no. 60/298,155, filed on June 13, 2001, and U.S. provisional patent application serial no. 60/335,936, filed on November 14, 2001, all of which are expressly incorporated by reference.

FIELD OF THE INVENTION

The field of the invention is cervical cancer, including diagnosis, characterization, management, and therapy of cervical cancer.

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BACKGROUND OF THE INVENTION

The increased number of cancer cases reported in the United States, and, indeed, around the world, is a major concern. Currently there are only a handful of treatments available for specific types of cancer, and these provide no absolute guarantee of success. In order to be most effective, these treatments require not only an early detection of the malignancy, but a reliable assessment of the severity of the malignancy.

Cancer of the cervix is one of the most common malignancies in women and remains a significant public health problem throughout the world. In the United States alone, invasive cervical cancer accounts for approximately 19% of all gynecological cancers. In 1996, it was estimated that there were 14,700 newly diagnosed cases and 4900 deaths attributed to this disease (American Cancer Society, Cancer Facts & Figures 1996, Atlanta, Ga.: American Cancer Society, 1996). In many developing countries, where mass screening programs are not widely available, the clinical problem is more serious. Worldwide, the number of new cases is estimated to be 471,000 with a four-year survival rate of only 40% (Munoz et al., 1989, *Epidemiology of Cervical Cancer* In: "Human Papillomavirus", New York, Oxford Press, pp 9-39; National Institutes of Health, Consensus Development Conference Statement on Cervical Cancer, Apr.1-3, 1996).

The precursor to cervical cancer is dysplasia, also known in the art as cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL). While it is not understood how normal cells become transformed, the concept of a continuous spectrum of histopathological change from normal, stratified epithelium through CIN to invasive cancer has been widely accepted for many years. A large body of epidemiological and molecular biological evidence has established human papillomavirus (HPV) infection as a causative factor in cervical cancer. HPV is found in 85% or more of squamous cell invasive lesions, which represent the most common histologic type seen in cervical carcinoma. Additional cofactors have also been identified, including oncogenes that have been activated by point mutations and chromosomal translocations or deletions.

In light of this, cervical cancer remains a highly preventable form of cancer when pre-invasive lesions are detected early. Cytological examination of Papanicolaou-stained cervical smears (also referred to as Pap smears) is currently the principle method for detecting cervical cancer. Not surprisingly, the effectiveness of Pap smear screening varies depending not only upon the quality of the sample being used, but also upon subjective parameters that are inherent to the analysis. In addition, despite the historical success of the test, concerns have arisen regarding its ability to reliably predict the behavior of some pre-invasive lesions (Ostor *et al.*, 1993, *Int. J. Gynecol. Pathol.* 12: 186-192; and Genest *et al.*, 1993, *Human Pathol.* 24: 730-736).

SUMMARY OF THE INVENTION

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The invention relates to cancer markers (hereinafter "markers" or "markers of the inventions"), which are listed in Table 1. The invention provides nucleic acids and proteins that are encoded by or correspond to the markers (hereinafter "marker nucleic acids" and "marker proteins," respectively). Table 1 provides the sequence identifiers of the sequences of such marker nucleic acids and proteins listed in the accompanying Sequence Listing. The invention further provides antibodies, antibody derivatives and antibody fragments which bind specifically with such proteins and/or fragments of the proteins.

The invention also relates to various methods, reagents and kits for diagnosing, staging, prognosing, monitoring and treating cervical cancer. "Cervical cancer" as used herein includes carcinomas, (e.g., carcinoma in situ, invasive

WO 02/101075 PCT/US02/18638

carcinoma, metastatic carcinoma) and pre-malignant conditions, (e.g., dysplasia, including CIN or SIL). In one embodiment, the invention provides a diagnostic method of assessing whether a patient has cervical cancer or has higher than normal risk for developing cervical cancer, comprising the steps of comparing the level of expression of a marker of the invention in a patient sample and the normal level of expression of the marker in a control, e.g., a sample from a patient without cervical cancer. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer or has higher than normal risk for developing cervical cancer.

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According to the invention, the markers are selected such that the positive predictive value of the methods of the invention is at least about 10%, preferably about 25%, more preferably about 50% and most preferably about 90%. Also preferred for use in the methods of the invention are markers that are differentially expressed, as compared to normal cervical cells, by at least two-fold in at least about 20%,more preferably about 50% and most preferably about 75% of any of the following conditions: stage 0 cervical cancer patients, stage I cervical cancer patients, stage II cervical cancer patients, grade I cervical cancer patients, grade I cervical cancer patients, grade II cervical cancer patients, squamous cell (epidermoid) cervical cancer patients, cervical adenocarcinoma patients, cervical adenosquamous carcinoma patients, small-cell cervical carcinoma patients, malignant cervical cancer patients with primary carcinomas of the cervix, patients with primary malignant lymphomas of the cervix and patients with secondary malignant lymphomas of the cervix, and all other types of cancers, malignancies and transformations associated with the cervix.

In a preferred diagnostic method of assessing whether a patient is afflicted with cervical cancer (*e.g.*, new detection ("screening"), detection of recurrence, reflex testing), the method comprises comparing:

- a) the level of expression of a marker of the invention in a patient sample, and
- b) the normal level of expression of the marker in a control non-cervical cancer sample.

WO 02/101075 PCT/US02/18638 - 4 -

A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer.

The invention also provides diagnostic methods for assessing the efficacy of a therapy for inhibiting cervical cancer in a patient. Such methods comprise comparing:

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- a) expression of a marker of the invention in a first sample obtained from the patient prior to providing at least a portion of the therapy to the patient, and
- b) expression of the marker in a second sample obtained from the patient following provision of the portion of the therapy.

A significantly lower level of expression of the marker in the second sample relative to that in the first sample is an indication that the therapy is efficacious for inhibiting cervical cancer in the patient.

It will be appreciated that in these methods the "therapy" may be any therapy for treating cervical cancer including, but not limited to, chemotherapy, radiation therapy, surgical removal of tumor tissue, gene therapy and biologic therapy such as the administering of antibodies and chemokines. Thus, the methods of the invention may be used to evaluate a patient before, during and after therapy, for example, to evaluate the reduction in tumor burden.

In a preferred embodiment, the diagnostic methods are directed to therapy using a chemical or biologic agent. These methods comprise comparing:

- a) expression of a marker of the invention in a first sample obtained from the patient and maintained in the presence of the chemical or biologic agent, and
- b) expression of the marker in a second sample obtained from the patient and maintained in the absence of the agent.

A significantly lower level of expression of the marker in the second sample relative to that in the first sample is an indication that the agent is efficacious for inhibiting cervical cancer, in the patient. In one embodiment, the first and second samples can be portions of a single sample obtained from the patient or portions of pooled samples obtained from the patient.

WO 02/101075 - 5 -

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PCT/US02/18638

The invention additionally provides a monitoring method for assessing the progression of cervical cancer in a patient, the method comprising:

- a) detecting in a patient sample at a first time point, the expression of a marker of the invention;
- b) repeating step a) at a subsequent time point in time; and
- c) comparing the level of expression detected in steps a) and b), and therefrom monitoring the progression of cervical cancer in the patient.

A significantly higher level of expression of the marker in the sample at the subsequent time point from that of the sample at the first time point is an indication that the cervical cancer has progressed, whereas a significantly lower level of expression is an indication that the cervical cancer has regressed.

The invention further provides a diagnostic method for determining whether cervical cancer has metastasized or is likely to metastasize in the future, the method comprising comparing:

- a) the level of expression of a marker of the invention in a patient sample, and
- b) the normal level (or non-metastatic level) of expression of the marker in a control sample.

A significantly higher level of expression in the patient sample as compared to the normal level (or non-metastatic level) is an indication that the cervical cancer has metastasized or is likely to metastasize in the future.

The invention moreover provides a test method for selecting a composition for inhibiting cervical cancer in a patient. This method comprises the steps of:

- a) obtaining a sample comprising cancer cells from the patient;
- b) separately maintaining aliquots of the sample in the presence of a plurality of test compositions;
- c) comparing expression of a marker of the invention in each of the aliquots; and
- d) selecting one of the test compositions which significantly reduces the level of expression of the marker in the aliquot containing that test composition, relative to the levels of expression of the marker in the presence of the other test compositions.

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The invention additionally provides a test method of assessing the cervical carcinogenic potential of a compound. This method comprises the steps of:

- a) maintaining separate aliquots of cervical cells in the presence and absence of the compound; and
- b) comparing expression of a marker of the invention in each of the aliquots.

A significantly higher level of expression of the marker in the aliquot maintained in the presence of the compound, relative to that of the aliquot maintained in the absence of the compound, is an indication that the compound possesses cervical carcinogenic potential.

In addition, the invention further provides a method of inhibiting cervical cancer in a patient. This method comprises the steps of:

- a) obtaining a sample comprising cancer cells from the patient;
- b) separately maintaining aliquots of the sample in the presence of a plurality of compositions;
- c) comparing expression of a marker of the invention in each of the aliquots; and
- d) administering to the patient at least one of the compositions which significantly lowers the level of expression of the marker in the aliquot containing that composition, relative to the levels of expression of the marker in the presence of the other compositions.

In the aforementioned methods, the samples or patient samples comprise cells obtained from the patient. The cells may be found in a cervical smear collected, for example, by a cervical brush. In another embodiment, the sample is a body fluid. Such fluids include, for example, blood fluids, lymph, ascitic fluids, gynecological fluids, urine, and fluids collected by vaginal rinsing. In a further embodiment, the patient sample is *in vivo*.

According to the invention, the level of expression of a marker of the invention in a sample can be assessed, for example, by detecting the presence in the sample of:

• the corresponding marker protein (e.g., a protein having one of the sequences set forth as "SEQ ID NO (AAs)" in Table 1, or a fragment of the protein (e.g. by using a reagent, such as an antibody, an antibody derivative,

WO 02/101075 PCT/US02/18638 - 7 -

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an antibody fragment or single-chain antibody, which binds specifically with the protein or protein fragment)

• the corresponding marker nucleic acid (e.g. a nucleotide transcript having one of the nucleic acid sequences set forth as "SEQ ID NO (nts)" in Table 1, or a complement thereof), or a fragment of the nucleic acid (e.g. by contacting transcribed polynucleotides obtained from the sample with a substrate having affixed thereto one or more nucleic acids having the entire or a segment of the nucleic acid sequence of any of the SEQ ID NO (nts), or a complement thereof)

• a metabolite which is produced directly (*i.e.*, catalyzed) or indirectly by the corresponding marker protein.

According to the invention, any of the aforementioned methods may be performed using a plurality (e.g. 2, 3, 5, or 10 or more) of cervical cancer markers, including cervical cancer markers known in the art. In such methods, the level of expression in the sample of each of a plurality of markers, at least one of which is a marker of the invention, is compared with the normal level of expression of each of the plurality of markers in samples of the same type obtained from control humans not afflicted with cervical cancer. A significantly altered (i.e., increased or decreased as specified in the above-described methods using a single marker) level of expression in the sample of one or more markers of the invention, or some combination thereof, relative to that marker's corresponding normal or control level, is an indication that the patient is afflicted with cervical cancer. For all of the aforementioned methods, the marker(s) are preferably selected such that the positive predictive value of the method is at least about 10%.

In a further aspect, the invention provides an antibody, an antibody derivative, or an antibody fragment, which binds specifically with a marker protein (e.g., a protein having one of the amino acid sequences set forth in the Sequence Listing) or a fragment of the protein. The invention also provides methods for making such antibody, antibody derivative, and antibody fragment. Such methods may comprise immunizing a mammal with a protein or peptide comprising the entirety, or a segment of 10 or more amino acids, of a marker protein (e.g., a protein having one of the amino acid sequences set forth in the Sequence Listing), wherein the protein or peptide may be obtained from a cell or by chemical synthesis. The methods of the invention also encompass producing

monoclonal and single-chain antibodies, which would further comprise isolating splenocytes from the immunized mammal, fusing the isolated splenocytes with an immortalized cell line to form hybridomas, and screening individual hybridomas for those that produce an antibody that binds specifically with a marker protein or a fragment of the protein.

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In another aspect, the invention relates to various diagnostic and test kits. In one embodiment, the invention provides a kit for assessing whether a patient is afflicted with cervical cancer. The kit comprises a reagent for assessing expression of a marker of the invention. In another embodiment, the invention provides a kit for assessing the suitability of a chemical or biologic agent for inhibiting cervical cancer in a patient. Such a kit comprises a reagent for assessing expression of a marker of the invention, and may also comprise one or more of such agents. In a further embodiment, the invention provides kits for assessing the presence of cervical cancer cells or treating cervical cancers. Such kits comprise an antibody, an antibody derivative, or an antibody fragment, which binds specifically with a marker protein, or a fragment of the protein. Such kits may also comprise a plurality of antibodies, antibody derivatives, or antibody fragments wherein the plurality of such antibody agents binds specifically with a marker protein, or a fragment of the protein.

In an additional embodiment, the invention also provides a kit for assessing the presence of cervical cancer cells, wherein the kit comprises a nucleic acid probe that binds specifically with a marker nucleic acid or a fragment of the nucleic acid. The kit may also comprise a plurality of probes, wherein each of the probes binds specifically with a marker nucleic acid, or a fragment of the nucleic acid.

In a further aspect, the invention relates to methods for treating a patient afflicted with cervical cancer or at risk of developing cervical cancer. Such methods may comprise reducing the expression and/or interfering with the biological function of a marker of the invention. In one embodiment, the method comprises providing to the patient an antisense oligonucleotide or polynucleotide complementary to a marker nucleic acid, or a segment thereof. For example, an antisense polynucleotide may be provided to the patient through the delivery of a vector that expresses an anti-sense polynucleotide of a marker nucleic acid or a fragment thereof. In another embodiment, the method comprises providing to the patient an antibody, an antibody derivative, or antibody fragment, which binds specifically with a marker protein or a fragment of the

protein. In a preferred embodiment, the antibody, antibody derivative or antibody fragment binds specifically with a protein having one of the amino acid sequences set forth in the Sequence Listing, or a fragment of the protein.

It will be appreciated that the methods and kits of the present invention may also include known cancer markers including known cervical cancer markers. It will further be appreciated that the methods and kits may be used to identify cancers other than cervical cancer.

DETAILED DESCRIPTION OF THE INVENTION

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The invention relates to newly discovered cancer markers associated with the cancerous state of cervical cells. It has been discovered that the higher than normal level of expression of any of these markers or combination of these markers correlates with the presence of cervical cancer including pre-malignant conditions such as dysplasia, in a patient. Methods are provided for detecting the presence of cervical cancer in a sample, the absence of cervical cancer in a sample, the stage of a cervical cancer, and other characteristics of cervical cancer that are relevant to prevention, diagnosis, characterization, and therapy of cervical cancer in a patient. Methods of treating cervical cancer are also provided.

Table 1 lists the markers of the invention which are over-expressed in cervical cancer cells compared to normal (*i.e.*, non-cancerous) cervical cells and comprises markers listed in Tables 2 and 3. Table 2 lists newly-identified nucleotide and amino acid sequences. Table 3 lists newly-identified nucleotide sequences. Tables 1-3 provide the sequence listing identifiers of the cDNA sequence of a nucleotide transcript and the amino acid sequence of a protein encoded by or corresponding to each marker, as well as the location of the protein coding sequence within the cDNA sequence.

Table 1

		SEQ ID NO	SEQ ID	
Marker	Gene Name	(nts)	NO (AAs)	CDS
M661	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 1	1	2	22311946
	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9,			22010.10
M662	variant 2	3	4	22311922
M663	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 3	5	6	22312000
M664	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 4	7	8	22311976
M1	APOL1: Apolipoprotein L-I mNA, splice variant A, major form	9	10	2131364
M2	APOL1: Apolipoprotein L-I mNA, splice variant B, minor form	11	12	2741518
M3	APOL3: apolipoprotein L, 3; TNF-inducible protein CG12-1	13	14	4181413
OV3	AQP5: Aquaporin 5	15	16	5191316
M4	BC001980: clone MGC:5618	17	18	157225
M5	BST2: Bone marrow stromal cell antigen 2	19	20	10552
M6	BTEB1: basic transcription element binding protein 1	21	22	12651999
1010	CD74: CD74 antigen (invariant polypeptide of major	21	22	12001999
M665	histocompatibility complex, class II antigen-associated)	23	24	8706
M7	CDC20: CDC20 cell cycle protein	25	26	451544
M8	CDKN2C: cyclin-dependent kinase inhibitor 2C, p18	27	28	12161722
IVIO	CKTSF1B1: (cysteine knot superfamily 1, BMP	21	20	12101722
M9	antagonist 1), gremlin	29	30	451544
M10	CLDN1: claudin 1	31	32	221856
M11	CLIC4: chloride intracellular channel 4	33	34	198959
M12	COL1A1: collagen, type I, alpha 1	35	36	1204514
M13	COL1A1: collagen, type I, alpha 1	37	38	1404240
M14	COLFA2: collageri, type I, alpha 2 COL8A1: collagen, type VIII, alpha 1	39	40	12235
M15	COPA: coatomer protein complex, subunit alpha			4674141
M16	CRIP1: cysteine-rich protein 1 (intestinal)	41 43	42 44	1234
M17	CTGF: connective tissue growth factor			
M18	DOC: downregulated in ovarian cancer 1	45 47	46	1461195
M19	EFNA1: ephrin-A1		48	1352393
M481		49	50	74691
	EPPK1: epiplakin 1	51	52	8915286
M20	FLJ11350: hypothetical protein FLJ11350	53	54	1061047
M21	FLJ13809: hypothetical protein FLJ13809	55	56	641593
M22	FLJ20500: hypothetical protein FLJ20500	57	58	198896
M23	FLJ23399: hypothetical protein FLJ23399	59	60	2831770
M24	FN1: Fibronectin 1, variant 1	61	62	<12384
M25	FN1: Fibronectin 1, variant 2	63	64	<16988
M482	FOSL2: FOS-like antigen 2, variant 1	65	66	3241304
M483	FOSL2: FOS-like antigen 2, variant 2	67	66	3241304
M484	FSHPRH1: FSH primary response (LRPR1, rat) homolog 1	68	69	2702540
M26	FY: Duffy blood group	70	71	4951511

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M485	G1P3:interferon, alpha-inducible protein (clone IFI-6-16)	72	73	108500
M486	GW112: GW112 protein	74	75	5091072
	HSKERUV: clone 266, Human radiated keratinocyte			
M27	mRNA 266 (keratin-related protein)	76	77	<1801
M28	HSPC121: butyrate-induced transcript 1	78	79	1501271
M29	HUMCLPB: Coactosin like protein	80	81	150576
M487	hypothetical protein	82	83	588163
M30	IFI27: (interferon, alpha-inducible protein 27	84	85	55423
OV31	IFI30: interferon, gamma-inducible protein 30	86	87	41952
M31	IFITM2: interferon induced transmembrane protein 2 (1-8D)	88	89	280678
M32	IGFBP-3: insulin-like growth factor binding protein 3	90	91	1331009
M33	IL8RA: interleukin 8	92	93	75374
M34	INHBA: Inhibin, beta-1	94	95	861366
M488	ITGA3: integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor), variant a	96	97	743229
	ITGA3: integrin, alpha 3 (antigen CD49C, alpha 3			
M454	subunit of VLA-3 receptor), variant b	98	99	743274
M35	ITGB6: integrin, beta 6	100	101	1952561
	KATII: L-kynurenine/alpha-aminoadipate			
M36	aminotransferase	102	103	4541731
M666	KCNAB1: potassium voltage-gated channel, shaker-related subfamily, beta member 1, variant 1	104	105	891315
M667	KCNAB1: potassium voltage-gated channel, shaker- related subfamily, beta member 1, variant 2	106	107	541313
M668	KCNAB1: potassium voltage-gated channel, shaker- related subfamily, beta member 1, variant 3	108	109	281233
M37	KIAA0662: KIAA0662 protein	110	111	<12035
M38	LAMA3: Laminin, alpha-3 (nicein (150kD), (kalinin (165kD), BM600 (150kD)	112	113	15142
M39	LAMC2: laminin, gamma 2	114	115	903671
M40	LSM5: U6 snRNA-associated Sm-like protein	116	117	1276
M41	LUM: lumican	118	119	851101
	MACMARCKS: macrophage myristoylated alanine-			
M42	rich C kinase substrate	120	121	14601
M43	MAGP: microfibrillar-associated protein 2 precursor, transcript variant 1	122	123	115666
M44	MAGP: microfibrillar-associated protein 2 precursor, transcript variant 2	124	125	100651
M45	MAPK: mitogen-activated protein kinase 1	126	127	3281410
M489	MCM6: minichromosome maintenance deficient (mis5, S. pombe) 6	128	129	622527
M46	MDK: midkine (neurite growth-promoting factor 2)	130	131	26457
M47	MGP: matrix Gla protein	132	133	47358
M48	MMP12: matrix metalloproteinase 12	134	135	131425
	MMP3: matrix metalloproteinase 3, stromelysin 1,	107	100	101720
M49	progelatinase	136	137	641497
M294	MMP7: matrix metalloproteinase 7 (matrilysin, uterine), PUMP1 proteinase, variant 1	138	139	48851
OV52	MMP7: matrix metalloproteinase 7 (matrilysin, uterine), PUMP1 proteinase, variant 2	140	139	28831

WO 02/101075 PCT/US02/18638 - 12 -

M50	MMP9: matrix metalloproteinase 9, gelatinase B, 92kD gelatinase, 92kD type IV collagenase	141	142	202143
OV68	MSLN: mesothelin, variant 1	143	144	882196
OV69	MSLN: mesothelin, variant 2	145	146	881980
OV70	MSLN: mesothelin, variant 3	147	148	881950
OV71	MSLN: mesothelin, variant 4	149	150	882172
OV72	MSLN: mesothelin, variant 5	151	152	881926
OV43	MSLN: mesothelin, variant 6	153	154	881956
OV45	MUC1: mucin 1, transmembrane, variant 1	155	156	581605
M669	MUC1: mucin 1, transmembrane, variant 2	157	158	743841
M51	MYBL2: v-myb avian myeloblastosis viral oncogene homolog-like 2	159	160	1282230
M52	MYH11: smooth muscle myosin heavy chain 11, isoform SM1	161	162	896007
M53	MYH11: smooth muscle myosin heavy chain 11, isoform SM2	163	164	895905
M54	NK4: natural killer cell transcript 4, variant 1	165	166	60764
M670	NK4: natural killer cell transcript 4, variant 2	167	168	60764
M55	NP25: (neuronal protein)	169	170	50898
OV48	OPN-a (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	171	172	1942
OV49	OPN-b (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	173	174	88990
OV50	OPN-c (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein 1	175	176	1861
M56	OSF-2, osteoblast specific factor 2 (fasciclin I-like), variant 1	177	178	122522
M491	OSF-2, osteoblast specific factor 2 (fasciclin I-like), variant 2	179	180	282367
M57	PIM2: pim-2 oncogene	181	182	1861190
M58	PLAU: plasminogen activator, urokinase	183	184	771372
M59	PLK: polo (Drosophia)-like kinase	185	186	641875
M671	PNN: pinin, desmosome associated protein	187	188	312262
M60	PRG1: proteoglycan 1, secretory granule	189	190	25501
M61	PTHLH: parathyroid hormone-like hormone	191	192	304831
M62	PTN: pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1)	193	194	15422048
M63	RAB6KIFL: RAB6 interacting, kinesin-like (rabkinesin6)	195	196	282700
M64	RARRES3: retinoic acid receptor responder (tazarotene induced) 3	197	198	62556
M65	RBP1: retinol-binding protein 1(cellular), CRABP-I, CRBP-I	199_	200	126533
M66	RGS16: Regulator of G protein signaling-16	201	202	93701
M67	S100A2: S100 calcium binding protein A2, variant 1	203	204	72362
M68	S100A2: S100 calcium binding protein A2, variant 2	205	206	41334
M69	SCYA20: small inducible cytokine subfamily A (Cys-Cys), member 20	207	208	59349
	SPARC: Osteonectin (secreted protein, acidic,			
M70	cysteine-rich) STCH: stress 70 protein chaperone, microsome-	209	210	58969
M71	associated	211	212	371452
M492	STK12: serine/ threonine kinase 12	213	214_	_ 581092

M72	TK1: thymidine kinase 1, soluble	215	216	58762
OV86	TMPRSS4: transmembrane protease, serine 4	217	218	3101623
M73	TMSB4X: thymosin, beta 4, X chromosome	219	220	78212
M74	TOP2A: topoisomerase (DNA) II alpha (170kD)	221	222	374632
M493	TPM1: tropomyosin 1 (alpha)	223	224	57911
M75	TXN: thioredoxin	225	226	64381
M76	UBCH10: ubiquitin carrier protein E2-C	227	228	41580
M77	UBD: diubiquitin	229	230	19516
M78	unnamed gene (1)	231	232	451353
M79	unnamed gene (2)	233	234	11508
M80	VATD: vacuolar proton pump delta polypeptide	235	236	166909
M81	ZWINT: ZW10 interactor	237	238	25858

Table 2

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9,	(110)	(, 5, 10)	2231194
M661	variant 1	1	2	6
	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9,			2231192
M662	variant 2	3	4	2
	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9,			2231200
M663	variant 3	5	6	0
	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9,			2231197
M664	variant 4	7	8	6
OV68	MSLN: mesothelin, variant 1	143	144	882196
OV69	MSLN: mesothelin, variant 2	145	146	881980
OV70	MSLN: mesothelin, variant 3	147	148	881950
OV71	MSLN: mesothelin, variant 4	149	150	882172
OV72	MSLN: mesothelin, variant 5	151	152	881926
M670	NK4: natural killer cell transcript 4, variant 2	167	168	60764
M67	S100A2: S100 calcium binding protein A2, variant 1	203	204	72362
OV86	TMPRSS4: transmembrane protease, serine 4	217	218	3101623
M78	unnamed gene (1)	231	232	451353
M79	unnamed gene (2)	233	234	11508

Table 3

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M481	EPPK1: epiplakin 1	51	52	8915286
M482	FOSL2: FOS-like antigen 2, variant 1	65	66	3241304
M483	FOSL2: FOS-like antigen 2, variant 2	67	66	3241304
M484	FSHPRH1: FSH primary response (LRPR1, rat) homolog 1	68	69	2702540
M35	ITGB6: integrin, beta 6	100	101	1952561
OV43	MSLN: mesothelin, variant 6	153	154	881956

Definitions

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As used herein, each of the following terms has the meaning associated with it in this section.

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.* to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

A "marker" is a gene whose altered level of expression in a tissue or cell from its expression level in normal or healthy tissue or cell is associated with a disease state, such as cancer. A "marker nucleic acid" is a nucleic acid (e.g., mRNA, cDNA) encoded by or corresponding to a marker of the invention. Such marker nucleic acids include DNA (e.g., cDNA) comprising the entire or a partial sequence of any of the nucleic acid sequences set forth in the Sequence Listing or the complement of such a sequence. The marker nucleic acids also include RNA comprising the entire or a partial sequence of any of the nucleic acid sequences set forth in the Sequence Listing or the complement of such a sequence, wherein all thymidine residues are replaced with uridine residues. A "marker protein" is a protein encoded by or corresponding to a marker of the invention. A marker protein comprises the entire or a partial sequence of any of the sequences set forth in the Sequence Listing. The terms "protein" and "polypeptide' are used interchangeably.

The term "probe" refers to any molecule which is capable of selectively binding to a specifically intended target molecule, for example, a nucleotide transcript or protein encoded by or corresponding to a marker. Probes can be either synthesized by one skilled in the art, or derived from appropriate biological preparations. For purposes of detection of the target molecule, probes may be specifically designed to be labeled, as

described herein. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

A "cervical-associated" body fluid is a fluid which, when in the body of a patient, contacts or passes through cervical cells or into which cells or proteins shed from cervical cells are capable of passing. The cells may be found in a cervical smear collected, for example, by a cervical brush. Exemplary cervical-associated body fluids include blood fluids, lymph, ascitic fluids, gynecological fluids, cystic fluid, urine, and fluids collected by vaginal rinsing.

The "normal" level of expression of a marker is the level of expression of the marker in cervical cells of a human subject or patient not afflicted with cervical cancer

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An "over-expression" or "significantly higher level of expression" of a marker refers to an expression level in a test sample that is greater than the standard error of the assay employed to assess expression, and is preferably at least twice, and more preferably three, four, five or ten times the expression level of the marker in a control sample (e.g., sample from a healthy subjects not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

A "significantly lower level of expression" of a marker refers to an expression level in a test sample that is at least twice, and more preferably three, four, five or ten times lower than the expression level of the marker in a control sample (*e.g.*, sample from a healthy subject not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

As used herein, the term "promoter/regulatory sequence" means a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue-specific manner.

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A "constitutive" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell under most or all physiological conditions of the cell.

An "inducible" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only when an inducer which corresponds to the promoter is present in the cell.

A "tissue-specific" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

A "transcribed polynucleotide" or "nucleotide transcript" is a polynucleotide (e.g. an mRNA, hnRNA, a cDNA, or an analog of such RNA or cDNA) which is complementary to or homologous with all or a portion of a mature mRNA made by transcription of a marker of the invention and normal post-transcriptional processing (e.g. splicing), if any, of the RNA transcript, and reverse transcription of the RNA transcript.

"Complementary" refers to the broad concept of sequence complementarity between regions of two nucleic acid strands or between two regions of the same nucleic acid strand. It is known that an adenine residue of a first nucleic acid region is capable of forming specific hydrogen bonds ("base pairing") with a residue of a second nucleic acid region which is antiparallel to the first region if the residue is thymine or uracil. Similarly, it is known that a cytosine residue of a first nucleic acid strand is capable of base pairing with a residue of a second nucleic acid strand which is antiparallel to the first strand if the residue is guanine. A first region of a nucleic acid is complementary to a second region of the same or a different nucleic acid if, when the two regions are arranged in an antiparallel fashion, at least one nucleotide residue of the first region comprises a first portion and the second region comprises a second portion, whereby, when the first and second portions are arranged in an antiparallel fashion, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residues of the first portion are capable of base pairing

with nucleotide residues in the second portion. More preferably, all nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion.

"Homologous" as used herein, refers to nucleotide sequence similarity between two regions of the same nucleic acid strand or between regions of two different nucleic acid strands. When a nucleotide residue position in both regions is occupied by the same nucleotide residue, then the regions are homologous at that position. A first region is homologous to a second region if at least one nucleotide residue position of each region is occupied by the same residue. Homology between two regions is expressed in terms of the proportion of nucleotide residue positions of the two regions that are occupied by the same nucleotide residue. By way of example, a region having the nucleotide sequence 5'-ATTGCC-3' and a region having the nucleotide sequence 5'-TATGGC-3' share 50% homology. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residue positions of each of the portions are occupied by the same nucleotide residue. More preferably, all nucleotide residue positions of each of the portions are occupied by the same nucleotide residue.

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A molecule is "fixed" or "affixed" to a substrate if it is covalently or non-covalently associated with the substrate such the substrate can be rinsed with a fluid (*e.g.* standard saline citrate, pH 7.4) without a substantial fraction of the molecule dissociating from the substrate.

As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in an organism found in nature.

A cancer is "inhibited" if at least one symptom of the cancer is alleviated, terminated, slowed, or prevented. As used herein, cervical cancer is also "inhibited" if recurrence or metastasis of the cancer is reduced, slowed, delayed, or prevented.

A kit is any manufacture (e.g. a package or container) comprising at least one reagent, e.g. a probe, for specifically detecting the expression of a marker of the invention. The kit may be promoted, distributed, or sold as a unit for performing the methods of the present invention.

WO 02/101075 PCT/US02/18638 - 18 -

"Proteins of the invention" encompass marker proteins and their fragments; variant marker proteins and their fragments; peptides and polypeptides comprising an at least 15 amino acid segment of a marker or variant marker protein; and fusion proteins comprising a marker or variant marker protein, or an at least 15 amino acid segment of a marker or variant marker protein.

Unless otherwise specified herewithin, the terms "antibody" and "antibodies" broadly encompass naturally-occurring forms of antibodies (e.g., IgG, IgA, IgM, IgE) and recombinant antibodies such as single-chain antibodies, chimeric and humanized antibodies and multi-specific antibodies, as well as fragments and derivatives of all of the foregoing, which fragments and derivatives have at least an antigenic binding site. Antibody derivatives may comprise a protein or chemical moiety conjugated to an antibody.

Description

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The present invention is based, in part, on newly identified markers which are over-expressed in cervical cancer cells as compared to their expression in normal (*i.e.* non-cancerous) cervical cells. The enhanced expression of one or more of these markers in cervical cells is herein correlated with the cancerous state of the tissue. The invention provides compositions, kits, and methods for assessing the cancerous state of cervical cells (*e.g.* cells obtained from a human, cultured human cells, archived or preserved human cells and *in vivo* cells) as well as treating patients afflicted with cervical cancer.

The compositions, kits, and methods of the invention have the following uses, among others:

- 1) assessing whether a patient is afflicted with cervical cancer;
- 2) assessing the stage of cervical cancer in a human patient:
- 3) assessing the grade of cervical cancer in a patient;
- 4) assessing the benign or malignant nature of cervical cancer in a patient;
- 5) assessing the metastatic potential of cervical cancer in a patient;
 - 6) assessing the histological type of neoplasm associated with cervical cancer in a patient;

WO 02/101075 PCT/US02/18638 - 19 -

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7) making antibodies, antibody fragments or antibody derivatives that are useful for treating cervical cancer and/or assessing whether a patient is afflicted with cervical cancer; 8) assessing the presence of cervical cancer cells; 9) assessing the efficacy of one or more test compounds for inhibiting cervical cancer in a patient; 10) assessing the efficacy of a therapy for inhibiting cervical cancer in a patient; 11) monitoring the progression of cervical cancer in a patient; 12) selecting a composition or therapy for inhibiting cervical cancer in a patient; 13) treating a patient afflicted with cervical cancer; 14) inhibiting cervical cancer in a patient; 15) assessing the cervical carcinogenic potential of a test compound;

16) preventing the onset of cervical cancer in a patient at risk for developing cervical cancer.

The invention thus includes a method of assessing whether a patient is afflicted with cervical cancer which includes assessing whether the patient has premetastasized cervical cancer. This method comprises comparing the level of expression of a marker of the invention (listed in Table 1) in a patient sample and the normal level of expression of the marker in a control, *e.g.*, a non-cervical cancer sample. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer.

and

Gene delivery vehicles, host cells and compositions (all described herein) containing nucleic acids comprising the entirety, or a segment of 15 or more nucleotides, of any of the nucleic acid sequences set forth in the Sequence Listing, or the complement of such sequences, and polypeptides comprising the entirety, or a segment of 10 or more amino acids, of any of the amino acid sequences set forth in the Sequence Listing, are also provided by this invention.

As described herein, cervical cancer in patients is associated with an increased level of expression of one or more markers of the invention. While, as discussed above, some of these changes in expression level result from occurrence of the

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cervical cancer, others of these changes induce, maintain, and promote the cancerous state of cervical cancer cells. Thus, cervical cancer characterized by an increase in the level of expression of one or more markers of the invention can be inhibited by reducing and/or interfering with the expression of the markers and/or function of the proteins encoded by those markers.

Expression of a marker of the invention can be inhibited in a number of ways generally known in the art. For example, an antisense oligonucleotide can be provided to the cervical cancer cells in order to inhibit transcription, translation, or both, of the marker(s). Alternately, a polynucleotide encoding an antibody, an antibody derivative, or an antibody fragment which specifically binds a marker protein, and operably linked with an appropriate promoter/regulator region, can be provided to the cell in order to generate intracellular antibodies which will inhibit the function or activity of the protein. The expression and/or function of a marker may also be inhibited by treating the cervical cancer cell with an antibody, antibody derivative or antibody fragment that specifically binds a marker protein. Using the methods described herein, a variety of molecules, particularly including molecules sufficiently small that they are able to cross the cell membrane, can be screened in order to identify molecules which inhibit expression of a marker or inhibit the function of a marker protein. The compound so identified can be provided to the patient in order to inhibit cervical cancer cells of the patient.

Any marker or combination of markers of the invention, as well as any known markers in combination with the markers of the invention, may be used in the compositions, kits, and methods of the present invention. In general, it is preferable to use markers for which the difference between the level of expression of the marker in cervical cancer cells and the level of expression of the same marker in normal cervical cells is as great as possible. Although this difference can be as small as the limit of detection of the method for assessing expression of the marker, it is preferred that the difference be at least greater than the standard error of the assessment method, and preferably a difference of at least 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 15-, 20-, 25-, 100-, 500-, 1000-fold or greater than the level of expression of the same marker in normal cervical tissue.

WO 02/101075 PCT/US02/18638 - 21 -

It is recognized that certain marker proteins are secreted from cervical cells (*i.e.* one or both of normal and cancerous cells) to the extracellular space surrounding the cells. These markers are preferably used in certain embodiments of the compositions, kits, and methods of the invention, owing to the fact that the such marker proteins can be detected in a cervical-associated body fluid sample, which may be more easily collected from a human patient than a tissue biopsy sample. In addition, preferred *in vivo* techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

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It is a simple matter for the skilled artisan to determine whether any particular marker protein is a secreted protein. In order to make this determination, the marker protein is expressed in, for example, a mammalian cell, preferably a human cervical cell line, extracellular fluid is collected, and the presence or absence of the protein in the extracellular fluid is assessed (*e.g.* using a labeled antibody which binds specifically with the protein).

The following is an example of a method which can be used to detect secretion of a protein. About 8 x 10⁵ 293T cells are incubated at 37°C in wells containing growth medium (Dulbecco's modified Eagle's medium {DMEM} supplemented with 10% fetal bovine serum) under a 5% (v/v) CO₂, 95% air atmosphere to about 60-70% confluence. The cells are then transfected using a standard transfection mixture comprising 2 micrograms of DNA comprising an expression vector encoding the protein and 10 microliters of LipofectAMINETM (GIBCO/BRL Catalog no. 18342-012) per well. The transfection mixture is maintained for about 5 hours, and then replaced with fresh growth medium and maintained in an air atmosphere. Each well is gently rinsed twice with DMEM which does not contain methionine or cysteine (DMEM-MC; ICN Catalog no. 16-424-54). About 1 milliliter of DMEM-MC and about 50 microcuries of Trans-³⁵STM reagent (ICN Catalog no. 51006) are added to each well. The wells are maintained under the 5% CO₂ atmosphere described above and incubated at 37°C for a selected period. Following incubation, 150 microliters of conditioned medium is removed and centrifuged to remove floating cells and debris.

WO 02/101075 PCT/US02/18638 - 22 -

The presence of the protein in the supernatant is an indication that the protein is secreted.

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It will be appreciated that patient samples containing cervical cells may be used in the methods of the present invention. In these embodiments, the level of expression of the marker can be assessed by assessing the amount (e.g. absolute amount or concentration) of the marker in a cervical cell sample, e.g., cervical smear obtained from a patient. The cell sample can, of course, be subjected to a variety of well-known post-collection preparative and storage techniques (e.g., nucleic acid and/or protein extraction, fixation, storage, freezing, ultrafiltration, concentration, evaporation, centrifugation, etc.) prior to assessing the amount of the marker in the sample. Likewise, cervical smears may also be subjected to post-collection preparative and storage techniques, e.g., fixation.

The compositions, kits, and methods of the invention can be used to detect expression of marker proteins having at least one portion which is displayed on the surface of cells which express it. It is a simple matter for the skilled artisan to determine whether a marker protein, or a portion thereof, is exposed on the cell surface. For example, immunological methods may be used to detect such proteins on whole cells, or well known computer-based sequence analysis methods may be used to predict the presence of at least one extracellular domain (*i.e.* including both secreted proteins and proteins having at least one cell-surface domain). Expression of a marker protein having at least one portion which is displayed on the surface of a cell which expresses it may be detected without necessarily lysing the cell (*e.g.* using a labeled antibody which binds specifically with a cell-surface domain of the protein).

Expression of a marker of the invention may be assessed by any of a wide variety of well known methods for detecting expression of a transcribed nucleic acid or protein. Non-limiting examples of such methods include immunological methods for detection of secreted, cell-surface, cytoplasmic, or nuclear proteins, protein purification methods, protein function or activity assays, nucleic acid hybridization methods, nucleic acid reverse transcription methods, and nucleic acid amplification methods.

In a preferred embodiment, expression of a marker is assessed using an antibody (e.g. a radio-labeled, chromophore-labeled, fluorophore-labeled, or enzyme-labeled antibody), an antibody derivative (e.g. an antibody conjugated with a substrate or with the protein or ligand of a protein-ligand pair {e.g. biotin-streptavidin} }, or an

antibody fragment (e.g. a single-chain antibody, an isolated antibody hypervariable domain, etc.) which binds specifically with a marker protein or fragment thereof, including a marker protein which has undergone all or a portion of its normal post-translational modification.

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In another preferred embodiment, expression of a marker is assessed by preparing mRNA/cDNA (*i.e.* a transcribed polynucleotide) from cells in a patient sample, and by hybridizing the mRNA/cDNA with a reference polynucleotide which is a complement of a marker nucleic acid, or a fragment thereof. cDNA can, optionally, be amplified using any of a variety of polymerase chain reaction methods prior to hybridization with the reference polynucleotide; preferably, it is not amplified. Expression of one or more markers can likewise be detected using quantitative PCR to assess the level of expression of the marker(s). Alternatively, any of the many known methods of detecting mutations or variants (*e.g.* single nucleotide polymorphisms, deletions, etc.) of a marker of the invention may be used to detect occurrence of a marker in a patient.

In a related embodiment, a mixture of transcribed polynucleotides obtained from the sample is contacted with a substrate having fixed thereto a polynucleotide complementary to or homologous with at least a portion (*e.g.* at least 7, 10, 15, 20, 25, 30, 40, 50, 100, 500, or more nucleotide residues) of a marker nucleic acid. If polynucleotides complementary to or homologous with are differentially detectable on the substrate (*e.g.* detectable using different chromophores or fluorophores, or fixed to different selected positions), then the levels of expression of a plurality of markers can be assessed simultaneously using a single substrate (*e.g.* a "gene chip" microarray of polynucleotides fixed at selected positions). When a method of assessing marker expression is used which involves hybridization of one nucleic acid with another, it is preferred that the hybridization be performed under stringent hybridization conditions.

Because the compositions, kits, and methods of the invention rely on detection of a difference in expression levels of one or more markers of the invention, it is preferable that the level of expression of the marker is significantly greater than the minimum detection limit of the method used to assess expression in at least one of normal cervical cells and cancerous cervical cells.

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It is understood that by routine screening of additional patient samples using one or more of the markers of the invention, it will be realized that certain of the markers are over-expressed in cancers of various types, including specific cervical cancers, as well as other cancers such as breast cancer, ovarian cancer, etc. For example, it will be confirmed that some of the markers of the invention are overexpressed in most (i.e. 50% or more) or substantially all (i.e. 80% or more) of cervical cancer. Furthermore, it will be confirmed that certain of the markers of the invention are associated with cervical cancer of various stages (i.e. stage 0, I, II, III, and IV cervical cancers, as well as subclassifications IA1, IA2, IB, IB1, IB2, IIA, IIB, IIIA, IIIB, IVA, and IVB, using the FIGO Stage Grouping system for primary carcinoma of the cervix (see Gynecologic Oncology, 1991, 41:199 and Cancer, 1992, 69:482)), and premalignant conditions (e.g., dysplasia including CIN or SIL), of various histologic subtypes (e.g. squamous cell carcinomas and squamous cell carcinoma variants such as verrucous carcinoma, lymphoepithelioma-like carcinoma, papillary squamous neoplasm and spindle cell squamous cell carcinoma (see Cervical Cancer and Preinvasive Neoplasia, 1996, pp. 90-91) serous, mucinous, endometrioid, and clear cell subtypes, as well as subclassifications and alternate classifications adenocarcinoma, papillary adenocarcinoma, papillary cystadenocarcinoma, surface papillary carcinoma, malignant adenofibroma, cystadenofibroma, adenocarcinoma, cystadenocarcinoma, adenoacanthoma, endometrioid stromal sarcoma, mesodermal {Müllerian} mixed tumor, malignant carcinoma, Brenner tumor, mixed epithelial tumor, and undifferentiated. carcinoma, using the WHO/FIGO system for classification of malignant cervical tumors; Scully, Atlas of Tumor Pathology, 3d series, Washington DC), and various grades (i.e. grade I {well differentiated}, grade II {moderately well differentiated}, and grade III {poorly differentiated from surrounding normal tissue}). In addition, as a greater number of patient samples are assessed for expression of the markers of the invention and the outcomes of the individual patients from whom the samples were obtained are correlated, it will also be confirmed that altered expression of certain of the markers of the invention are strongly correlated with malignant cancers and that altered expression of other markers of the invention are strongly correlated with benign tumors. The compositions, kits, and methods of the invention are thus useful for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of cervical cancer in patients.

When the compositions, kits, and methods of the invention are used for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of cervical cancer in a patient, it is preferred that the marker or panel of markers of the invention is selected such that a positive result is obtained in at least about 20%, and preferably at least about 40%, 60%, or 80%, and more preferably in substantially all patients afflicted with a cervical cancer of the corresponding stage, grade, histological type, or benign/malignant nature. Preferably, the marker or panel of markers of the invention is selected such that a positive predictive value (PPV) of greater than about 10% is obtained for the general population (more preferably coupled with an assay specificity greater than 80%).

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When a plurality of markers of the invention are used in the compositions, kits, and methods of the invention, the level of expression of each marker in a patient sample can be compared with the normal level of expression of each of the plurality of markers in non-cancerous samples of the same type, either in a single reaction mixture (*i.e.* using reagents, such as different fluorescent probes, for each marker) or in individual reaction mixtures corresponding to one or more of the markers. In one embodiment, a significantly increased level of expression of more than one of the plurality of markers in the sample, relative to the corresponding normal levels, is an indication that the patient is afflicted with cervical cancer. When a plurality of markers is used, it is preferred that 2, 3, 4, 5, 8, 10, 12, 15, 20, 30, or 50 or more individual markers be used, wherein fewer markers are preferred.

In order to maximize the sensitivity of the compositions, kits, and methods of the invention (*i.e.* by interference attributable to cells of non-cervical origin in a patient sample), it is preferable that the marker of the invention used therein be a marker which has a restricted tissue distribution, *e.g.*, normally not expressed in a non-cervical tissue.

Only a small number of markers are known to be associated with cervical cancer (e.g. bcl-2, 15A8 antigen, cdc6, Mcm5, and EGFR). These markers are not, of course, included among the markers of the invention, although they may be used together with one or more markers of the invention in a panel of markers, for example. It is well known that certain types of genes, such as oncogenes, tumor suppressor genes, growth factor-like genes, protease-like genes, and protein kinase-like genes are often involved with development of cancers of various types. Thus, among the markers of the

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invention, use of those which correspond to proteins which resemble known proteins encoded by known oncogenes and tumor suppressor genes, and those which correspond to proteins which resemble growth factors, proteases, and protein kinases are preferred.

It is recognized that the compositions, kits, and methods of the invention will be of particular utility to patients having an enhanced risk of developing cervical cancer and their medical advisors. Patients recognized as having an enhanced risk of developing cervical cancer include, for example, patients having a familial history of cervical cancer, patients identified as having a mutant oncogene (*i.e.* at least one allele), and patients of advancing age (*i.e.* women older than about 50 or 60 years).

The level of expression of a marker in normal (*i.e.* non-cancerous) human cervical tissue can be assessed in a variety of ways. In one embodiment, this normal level of expression is assessed by assessing the level of expression of the marker in a portion of cervical cells which appears to be non-cancerous and by comparing this normal level of expression with the level of expression in a portion of the cervical cells which is suspected of being cancerous. Alternately, and particularly as further information becomes available as a result of routine performance of the methods described herein, population-average values for normal expression of the markers of the invention may be used. In other embodiments, the 'normal' level of expression of a marker may be determined by assessing expression of the marker in a patient sample obtained from a non-cancer-afflicted patient, from a patient sample obtained from a patient before the suspected onset of cervical cancer in the patient, from archived patient samples, and the like.

The invention includes compositions, kits, and methods for assessing the presence of cervical cancer cells in a sample (e.g. an archived tissue sample or a sample obtained from a patient). These compositions, kits, and methods are substantially the same as those described above, except that, where necessary, the compositions, kits, and methods are adapted for use with samples other than patient samples. For example, when the sample to be used is a parafinized, archived human tissue sample, it can be necessary to adjust the ratio of compounds in the compositions of the invention, in the kits of the invention, or the methods used to assess levels of marker expression in the sample. Such methods are well known in the art and within the skill of the ordinary artisan.

The invention includes a kit for assessing the presence of cervical cancer cells (*e.g.* in a sample such as a patient sample). The kit comprises a plurality of reagents, each of which is capable of binding specifically with a marker nucleic acid or protein. Suitable reagents for binding with a marker protein include antibodies, antibody derivatives, antibody fragments, and the like. Suitable reagents for binding with a marker nucleic acid (*e.g.* a genomic DNA, an mRNA, a spliced mRNA, a cDNA, or the like) include complementary nucleic acids. For example, the nucleic acid reagents may include oligonucleotides (labeled or non-labeled) fixed to a substrate, labeled oligonucleotides not bound with a substrate, pairs of PCR primers, molecular beacon probes, and the like.

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The kit of the invention may optionally comprise additional components useful for performing the methods of the invention. By way of example, the kit may comprise fluids (e.g. SSC buffer) suitable for annealing complementary nucleic acids or for binding an antibody with a protein with which it specifically binds, one or more sample compartments, an instructional material which describes performance of a method of the invention, a sample of normal cervical cells, a sample of cervical cancer cells, and the like.

The invention also includes a method of making an isolated hybridoma which produces an antibody useful for assessing whether patient is afflicted with an cervical cancer. In this method, a protein or peptide comprising the entirety or a segment of a marker protein is synthesized or isolated (e.g. by purification from a cell in which it is expressed or by transcription and translation of a nucleic acid encoding the protein or peptide in vivo or in vitro using known methods). A vertebrate, preferably a mammal such as a mouse, rat, rabbit, or sheep, is immunized using the protein or peptide. The vertebrate may optionally (and preferably) be immunized at least one additional time with the protein or peptide, so that the vertebrate exhibits a robust immune response to the protein or peptide. Splenocytes are isolated from the immunized vertebrate and fused with an immortalized cell line to form hybridomas, using any of a variety of methods well known in the art. Hybridomas formed in this manner are then screened using standard methods to identify one or more hybridomas which produce an antibody which specifically binds with the marker protein or a fragment thereof. The invention also includes hybridomas made by this method and antibodies made using such hybridomas.

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The invention also includes a method of assessing the efficacy of a test compound for inhibiting cervical cancer cells. As described above, differences in the level of expression of the markers of the invention correlate with the cancerous state of cervical cells. Although it is recognized that changes in the levels of expression of certain of the markers of the invention likely result from the cancerous state of cervical cells, it is likewise recognized that changes in the levels of expression of other of the markers of the invention induce, maintain, and promote the cancerous state of those cells. Thus, compounds which inhibit an cervical cancer in a patient will cause the level of expression of one or more of the markers of the invention to change to a level nearer the normal level of expression for that marker (*i.e.* the level of expression for the marker in non-cancerous cervical cells).

This method thus comprises comparing expression of a marker in a first cervical cell sample and maintained in the presence of the test compound and expression of the marker in a second cervical cell sample and maintained in the absence of the test compound. A significantly reduced expression of a marker of the invention in the presence of the test compound is an indication that the test compound inhibits cervical cancer. The cervical cell samples may, for example, be aliquots of a single sample of normal cervical cells obtained from a patient, pooled samples of normal cervical cells obtained from a patient, cells of a normal cervical cell line, aliquots of a single sample of cervical cancer cells obtained from a patient, pooled samples of cervical cancer cells obtained from a patient, cells of an cervical cancer cell line, or the like. In one embodiment, the samples are cervical cancer cells obtained from a patient and a plurality of compounds known to be effective for inhibiting various cervical cancers are tested in order to identify the compound which is likely to best inhibit the cervical cancer in the patient.

This method may likewise be used to assess the efficacy of a therapy for inhibiting cervical cancer in a patient. In this method, the level of expression of one or more markers of the invention in a pair of samples (one subjected to the therapy, the other not subjected to the therapy) is assessed. As with the method of assessing the efficacy of test compounds, if the therapy induces a significantly lower level of expression of a marker of the invention then the therapy is efficacious for inhibiting cervical cancer. As above, if samples from a selected patient are used in this method,

then alternative therapies can be assessed *in vitro* in order to select a therapy most likely to be efficacious for inhibiting cervical cancer in the patient.

As described above, the cancerous state of human cervical cells is correlated with changes in the levels of expression of the markers of the invention. The invention includes a method for assessing the human cervical cell carcinogenic potential of a test compound. This method comprises maintaining separate aliquots of human cervical cells in the presence and absence of the test compound. Expression of a marker of the invention in each of the aliquots is compared. A significantly higher level of expression of a marker of the invention in the aliquot maintained in the presence of the test compound (relative to the aliquot maintained in the absence of the test compound) is an indication that the test compound possesses human cervical cell carcinogenic potential. The relative carcinogenic potentials of various test compounds can be assessed by comparing the degree of enhancement or inhibition of the level of expression of the relevant markers, by comparing the number of markers for which the level of expression is enhanced or inhibited, or by comparing both.

Various aspects of the invention are described in further detail in the following subsections.

I. Isolated Nucleic Acid Molecules

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One aspect of the invention pertains to isolated nucleic acid molecules, including nucleic acids which encode a marker protein or a portion thereof. Isolated nucleic acids of the invention also include nucleic acid molecules sufficient for use as hybridization probes to identify marker nucleic acid molecules, and fragments of marker nucleic acid molecules, *e.g.*, those suitable for use as PCR primers for the amplification or mutation of marker nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Preferably, an "isolated" nucleic acid molecule is free of sequences (preferably protein-encoding sequences) which naturally flank the nucleic acid (*i.e.*,

sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kB, 4 kB, 3 kB, 2 kB, 1 kB, 0.5 kB or 0.1 kB of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the present invention can be isolated using standard molecular biology techniques and the sequence information in the database records described herein. Using all or a portion of such nucleic acid sequences, nucleic acid molecules of the invention can be isolated using standard hybridization and cloning techniques (e.g., as described in Sambrook et al., ed., Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

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A nucleic acid molecule of the invention can be amplified using cDNA, mRNA, or genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, nucleotides corresponding to all or a portion of a nucleic acid molecule of the invention can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which has a nucleotide sequence complementary to the nucleotide sequence of a marker nucleic acid or to the nucleotide sequence of a nucleic acid encoding a marker protein. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given nucleotide sequence thereby forming a stable duplex.

Moreover, a nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence, wherein the full length nucleic acid sequence comprises a marker nucleic acid or which encodes a marker protein. Such nucleic acids

can be used, for example, as a probe or primer. The probe/primer typically is used as one or more substantially purified oligonucleotides. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 7, preferably about 15, more preferably about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 or more consecutive nucleotides of a nucleic acid of the invention.

Probes based on the sequence of a nucleic acid molecule of the invention can be used to detect transcripts or genomic sequences corresponding to one or more markers of the invention. The probe comprises a label group attached thereto, *e.g.*, a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as part of a diagnostic test kit for identifying cells or tissues which misexpress the protein, such as by measuring levels of a nucleic acid molecule encoding the protein in a sample of cells from a subject, *e.g.*, detecting mRNA levels or determining whether a gene encoding the protein has been mutated or deleted.

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The invention further encompasses nucleic acid molecules that differ, due to degeneracy of the genetic code, from the nucleotide sequence of nucleic acids encoding a marker protein (e.g., a protein having one of the amino acid sequences set forth in the Sequence Listing), and thus encode the same protein.

It will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequence can exist within a population (e.g., the human population). Such genetic polymorphisms can exist among individuals within a population due to natural allelic variation. An allele is one of a group of genes which occur alternatively at a given genetic locus. In addition, it will be appreciated that DNA polymorphisms that affect RNA expression levels can also exist that may affect the overall expression level of that gene (e.g., by affecting regulation or degradation).

As used herein, the phrase "allelic variant" refers to a nucleotide sequence which occurs at a given locus or to a polypeptide encoded by the nucleotide sequence.

As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding a polypeptide corresponding to a marker of the invention. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be

WO 02/101075 PCT/US02/18638 - 32 -

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readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

In another embodiment, an isolated nucleic acid molecule of the invention is at least 7, 15, 20, 25, 30, 40, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 550, 650, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3500, 4000, 4500, or more nucleotides in length and hybridizes under stringent conditions to a marker nucleic acid or to a nucleic acid encoding a marker protein. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% (65%, 70%, preferably 75%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in sections 6.3.1-6.3.6 of *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989). A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65°C.

In addition to naturally-occurring allelic variants of a nucleic acid molecule of the invention that can exist in the population, the skilled artisan will further appreciate that sequence changes can be introduced by mutation thereby leading to changes in the amino acid sequence of the encoded protein, without altering the biological activity of the protein encoded thereby. For example, one can make nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are not conserved or only semi-conserved among homologs of various species may be non-essential for activity and thus would be likely targets for alteration.

Alternatively, amino acid residues that are conserved among the homologs of various species (e.g., murine and human) may be essential for activity and thus would not be likely targets for alteration.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a variant marker protein that contain changes in amino acid residues that are not essential for activity. Such variant marker proteins differ in amino acid sequence from the naturally-occurring marker proteins, yet retain biological activity. In one embodiment, such a variant marker protein has an amino acid sequence that is at least about 40% identical, 50%, 60%, 70%, 80%, 90%, 95%, or 98% identical to the amino acid sequence of a marker protein.

An isolated nucleic acid molecule encoding a variant marker protein can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of marker nucleic acids, such that one or more amino acid residue substitutions, additions, or deletions are introduced into the encoded protein. Mutations can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), non-polar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

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The present invention encompasses antisense nucleic acid molecules, *i.e.*, molecules which are complementary to a sense nucleic acid of the invention, *e.g.*, complementary to the coding strand of a double-stranded marker cDNA molecule or complementary to a marker mRNA sequence. Accordingly, an antisense nucleic acid of the invention can hydrogen bond to (*i.e.* anneal with) a sense nucleic acid of the invention. The antisense nucleic acid can be complementary to an entire coding strand,

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or to only a portion thereof, *e.g.*, all or part of the protein coding region (or open reading frame). An antisense nucleic acid molecule can also be antisense to all or part of a non-coding region of the coding strand of a nucleotide sequence encoding a marker protein. The non-coding regions ("5' and 3' untranslated regions") are the 5' and 3' sequences which flank the coding region and are not translated into amino acids.

An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 or more nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been sub-cloned in an antisense orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated in situ such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a marker protein to thereby inhibit expression of the marker, e.g., by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. Examples of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site or infusion of the antisense nucleic acid into an ovary-associated body fluid. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, e.g., by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

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An antisense nucleic acid molecule of the invention can be an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual α-units, the strands run parallel to each other (Gaultier *et al.*, 1987, *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue *et al.*, 1987, *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.*, 1987, *FEBS Lett.* 215:327-330).

The invention also encompasses ribozymes. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (e.g., hammerhead ribozymes as described in Haselhoff and Gerlach, 1988, *Nature* 334:585-591) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. A ribozyme having specificity for a nucleic acid molecule encoding a marker protein can be designed based

upon the nucleotide sequence of a cDNA corresponding to the marker. For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved (see Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742).

Alternatively, an mRNA encoding a polypeptide of the invention can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (see, *e.g.*, Bartel and Szostak, 1993, *Science* 261:1411-1418).

The invention also encompasses nucleic acid molecules which form triple helical structures. For example, expression of a marker of the invention can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the gene encoding the marker nucleic acid or protein (*e.g.*, the promoter and/or enhancer) to form triple helical structures that prevent transcription of the gene in target cells. See generally Helene (1991) *Anticancer Drug Des.* 6(6):569-84; Helene (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher (1992) *Bioassays* 14(12):807-15.

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In various embodiments, the nucleic acid molecules of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see Hyrup *et al.*, 1996, *Bioorganic & Medicinal Chemistry* 4(1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup *et al.* (1996), *supra*; Perry-O'Keefe *et al.* (1996) *Proc. Natl. Acad. Sci. USA* 93:14670-675.

PNAs can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, *e.g.*, inducing transcription or translation arrest or inhibiting replication. PNAs can also be used, *e.g.*, in the analysis of single base pair mutations in a gene by, *e.g.*, PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, *e.g.*, S1 nucleases (Hyrup

(1996), *supra*; or as probes or primers for DNA sequence and hybridization (Hyrup, 1996, *supra*; Perry-O'Keefe *et al.*, 1996, *Proc. Natl. Acad. Sci. USA* 93:14670-675).

In another embodiment, PNAs can be modified, e.g., to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated which can combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, e.g., RNase H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup, 1996, supra). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996), supra, and Finn et al. (1996) Nucleic Acids Res. 24(17):3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite can be used as a link between the PNA and the 5' end of DNA (Mag et al., 1989, Nucleic Acids Res. 17:5973-88). PNA monomers are then coupled in a step-wise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn et al., 1996, Nucleic Acids Res. 24(17):3357-63). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser et al., 1975, Bioorganic Med. Chem. Lett. 5:1119-11124).

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In other embodiments, the oligonucleotide can include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents

25 facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, 1989, *Proc.*Natl. Acad. Sci. USA 86:6553-6556; Lemaitre *et al.*, 1987, Proc. Natl. Acad. Sci. USA 84:648-652; PCT Publication No. WO 88/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, 1988, Bio/Techniques

30 6:958-976) or intercalating agents (see, *e.g.*, Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide can be conjugated to another molecule, *e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The invention also includes molecular beacon nucleic acids having at least one region which is complementary to a nucleic acid of the invention, such that the molecular beacon is useful for quantitating the presence of the nucleic acid of the invention in a sample. A "molecular beacon" nucleic acid is a nucleic acid comprising a pair of complementary regions and having a fluorophore and a fluorescent quencher associated therewith. The fluorophore and quencher are associated with different portions of the nucleic acid in such an orientation that when the complementary regions are annealed with one another, fluorescence of the fluorophore is quenched by the quencher. When the complementary regions of the nucleic acid are not annealed with one another, fluorescence of the fluorophore is quenched to a lesser degree. Molecular beacon nucleic acids are described, for example, in U.S. Patent 5.876,930.

II. Isolated Proteins and Antibodies

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One aspect of the invention pertains to isolated marker proteins and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a marker protein or a fragment thereof. In one embodiment, the native marker protein can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, a protein or peptide comprising the whole or a segment of the marker protein is produced by recombinant DNA techniques. Alternative to recombinant expression, such protein or peptide can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is substantially free of cellular material includes preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less

than about 20%, 10%, or 5% of the volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

Biologically active portions of a marker protein include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the marker protein, which include fewer amino acids than the full length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding full-length protein. A biologically active portion of a marker protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in which other regions of the marker protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of the marker protein.

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Preferred marker proteins are encoded by nucleotide sequences comprising the sequence of any of the sequences set forth in the Sequence Listing. Other useful proteins are substantially identical (e.g., at least about 40%, preferably 50%, 60%, 70%, 80%, 90%, 95%, or 99%) to one of these sequences and retain the functional activity of the corresponding naturally-occurring marker protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

To determine the percent identity of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., %

identity = # of identical positions/total # of positions (e.g., overlapping positions) x100). In one embodiment the two sequences are the same length.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) Proc. Natl. Acad. Sci. USA 87:2264-2268, modified as in Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90:5873-5877. Such an algorithm is incorporated into the BLASTN and BLASTX programs of Altschul, et al. (1990) J. Mol. Biol. 215:403-410. BLAST nucleotide searches can be performed with the BLASTN program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTP program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, a newer version of the BLAST algorithm called Gapped BLAST can be utilized as described in Altschul et al. (1997) Nucleic Acids Res. 15 25:3389-3402, which is able to perform gapped local alignments for the programs BLASTN, BLASTP and BLASTX. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (e.g., BLASTX and BLASTN) can be used. See 20 http://www.ncbi.nlm.nih.gov. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) CABIOS 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a 25 PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) Proc. Natl. Acad. Sci. USA 85:2444-2448. When using the FASTA algorithm for comparing nucleotide or amino acid sequences, a PAM120 weight residue table can, for 30 example, be used with a k-tuple value of 2.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

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The invention also provides chimeric or fusion proteins comprising a marker protein or a segment thereof. As used herein, a "chimeric protein" or "fusion protein" comprises all or part (preferably a biologically active part) of a marker protein operably linked to a heterologous polypeptide (*i.e.*, a polypeptide other than the marker protein). Within the fusion protein, the term "operably linked" is intended to indicate that the marker protein or segment thereof and the heterologous polypeptide are fused in-frame to each other. The heterologous polypeptide can be fused to the aminoterminus or the carboxyl-terminus of the marker protein or segment.

One useful fusion protein is a GST fusion protein in which a marker protein or segment is fused to the carboxyl terminus of GST sequences. Such fusion proteins can facilitate the purification of a recombinant polypeptide of the invention.

In another embodiment, the fusion protein contains a heterologous signal sequence at its amino terminus. For example, the native signal sequence of a marker protein can be removed and replaced with a signal sequence from another protein. For example, the gp67 secretory sequence of the baculovirus envelope protein can be used as a heterologous signal sequence (Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, 1992). Other examples of eukaryotic heterologous signal sequences include the secretory sequences of melittin and human placental alkaline phosphatase (Stratagene; La Jolla, California). In yet another example, useful prokaryotic heterologous signal sequences include the phoA secretory signal (Sambrook *et al.*, *supra*) and the protein A secretory signal (Pharmacia Biotech; Piscataway, New Jersey).

In yet another embodiment, the fusion protein is an immunoglobulin fusion protein in which all or part of a marker protein is fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a ligand (soluble or membrane-bound) and a protein on the surface of a cell (receptor), to thereby suppress signal transduction *in vivo*. The immunoglobulin fusion protein can be used to affect the bioavailability of a cognate ligand of a marker protein. Inhibition of ligand/receptor interaction can be

WO 02/101075 PCT/US02/18638 - 42 -

useful therapeutically, both for treating proliferative and differentiative disorders and for modulating (e.g. promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies directed against a marker protein in a subject, to purify ligands and in screening assays to identify molecules which inhibit the interaction of the marker protein with ligands.

Chimeric and fusion proteins of the invention can be produced by standard recombinant DNA techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see, e.g., Ausubel et al., supra). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST polypeptide). A nucleic acid encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide of the invention.

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A signal sequence can be used to facilitate secretion and isolation of marker proteins. Signal sequences are typically characterized by a core of hydrophobic amino acids which are generally cleaved from the mature protein during secretion in one or more cleavage events. Such signal peptides contain processing sites that allow cleavage of the signal sequence from the mature proteins as they pass through the secretory pathway. Thus, the invention pertains to marker proteins, fusion proteins or segments thereof having a signal sequence, as well as to such proteins from which the signal sequence has been proteolytically cleaved (i.e., the cleavage products). In one embodiment, a nucleic acid sequence encoding a signal sequence can be operably linked in an expression vector to a protein of interest, such as a marker protein or a segment thereof. The signal sequence directs secretion of the protein, such as from a eukaryotic host into which the expression vector is transformed, and the signal sequence is subsequently or concurrently cleaved. The protein can then be readily purified from the extracellular medium by art recognized methods. Alternatively, the signal sequence can be linked to the protein of interest using a sequence which facilitates purification, such as with a GST domain.

The present invention also pertains to variants of the marker proteins. Such variants have an altered amino acid sequence which can function as either agonists (mimetics) or as antagonists. Variants can be generated by mutagenesis, *e.g.*, discrete point mutation or truncation. An agonist can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of the protein. An antagonist of a protein can inhibit one or more of the activities of the naturally occurring form of the protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the protein of interest. Thus, specific biological effects can be elicited by treatment with a variant of limited function.

Treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein can have fewer side effects in a subject relative to treatment with the naturally occurring form of the protein.

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Variants of a marker protein which function as either agonists (mimetics) or as antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*, truncation mutants, of the protein of the invention for agonist or antagonist activity. In one embodiment, a variegated library of variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential protein sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display). There are a variety of methods which can be used to produce libraries of potential variants of the marker proteins from a degenerate oligonucleotide sequence. Methods for synthesizing degenerate oligonucleotides are known in the art (see, *e.g.*, Narang, 1983, *Tetrahedron* 39:3; Itakura *et al.*, 1984, *Annu. Rev. Biochem.* 53:323; Itakura *et al.*, 1984, *Science* 198:1056; Ike *et al.*, 1983 *Nucleic Acid Res.* 11:477).

In addition, libraries of segments of a marker protein can be used to generate a variegated population of polypeptides for screening and subsequent selection of variant marker proteins or segments thereof. For example, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of the coding sequence of interest with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different

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nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes amino terminal and internal fragments of various sizes of the protein of interest.

Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify variants of a protein of the invention (Arkin and Yourvan, 1992, *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.*, 1993, *Protein Engineering* 6(3):327-331).

Another aspect of the invention pertains to antibodies directed against a protein of the invention. In preferred embodiments, the antibodies specifically bind a marker protein or a fragment thereof. The terms "antibody" and "antibodies" as used interchangeably herein refer to immunoglobulin molecules as well as fragments and derivatives thereof that comprise an immunologically active portion of an immunoglobulin molecule, (*i.e.*, such a portion contains an antigen binding site which specifically binds an antigen, such as a marker protein, *e.g.*, an epitope of a marker protein). An antibody which specifically binds to a protein of the invention is an antibody which binds the protein, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the protein. Examples of an immunologically active portion of an immunoglobulin molecule include, but are not limited to, single-chain antibodies (scAb), F(ab) and F(ab')₂ fragments.

An isolated protein of the invention or a fragment thereof can be used as an immunogen to generate antibodies. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments for use as immunogens. The antigenic peptide of a protein of the invention comprises at least 8 (preferably 10, 15, 20, or 30 or more) amino acid residues of the amino acid sequence of one of the

WO 02/101075 PCT/US02/18638 - 45 -

proteins of the invention, and encompasses at least one epitope of the protein such that an antibody raised against the peptide forms a specific immune complex with the protein. Preferred epitopes encompassed by the antigenic peptide are regions that are located on the surface of the protein, *e.g.*, hydrophilic regions. Hydrophobicity sequence analysis, hydrophilicity sequence analysis, or similar analyses can be used to identify hydrophilic regions. In preferred embodiments, an isolated marker protein or fragment thereof is used as an immunogen.

An immunogen typically is used to prepare antibodies by immunizing a suitable (*i.e.* immunocompetent) subject such as a rabbit, goat, mouse, or other mammal or vertebrate. An appropriate immunogenic preparation can contain, for example, recombinantly-expressed or chemically-synthesized protein or peptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or a similar immunostimulatory agent. Preferred immunogen compositions are those that contain no other human proteins such as, for example, immunogen compositions made using a non-human host cell for recombinant expression of a protein of the invention. In such a manner, the resulting antibody compositions have reduced or no binding of human proteins other than a protein of the invention.

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The invention provides polyclonal and monoclonal antibodies. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope. Preferred polyclonal and monoclonal antibody compositions are ones that have been selected for antibodies directed against a protein of the invention. Particularly preferred polyclonal and monoclonal antibody preparations are ones that contain only antibodies directed against a marker protein or fragment thereof.

Polyclonal antibodies can be prepared by immunizing a suitable subject with a protein of the invention as an immunogen. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. At an appropriate time after immunization, *e.g.*, when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies (mAb) by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497, the human B cell

hybridoma technique (see Kozbor et al., 1983, Immunol. Today 4:72), the EBV-hybridoma technique (see Cole et al., pp. 77-96 In Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc., 1985) or trioma techniques. The technology for producing hybridomas is well known (see generally Current Protocols in Immunology, Coligan et al. ed., John Wiley & Sons, New York, 1994). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, e.g., using a standard ELISA assay.

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Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a protein of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275- 1281; Griffiths *et al.* (1993) *EMBO J.* 12:725-734.

The invention also provides recombinant antibodies that specifically bind a protein of the invention. In preferred embodiments, the recombinant antibodies specifically binds a marker protein or fragment thereof. Recombinant antibodies include, but are not limited to, chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, single-chain antibodies and multispecific antibodies. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, *e.g.*, Cabilly et al., U.S. Patent No. 4,816,567; and Boss et al., U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Single-chain antibodies have an

antigen binding site and consist of a single polypeptide. They can be produced by techniques known in the art, for example using methods described in Ladner *et. al* U.S. Pat. No. 4,946,778 (which is incorporated herein by reference in its entirety); Bird *et al.*, (1988) *Science* 242:423-426; Whitlow *et al.*, (1991) *Methods in Enzymology* 2:1-9; Whitlow *et al.*, (1991) *Methods in Enzymology* 2:97-105; and Huston *et al.*, (1991) *Methods in Enzymology Molecular Design and Modeling: Concepts and Applications* 203:46-88. Multi-specific antibodies are antibody molecules having at least two antigen-binding sites that specifically bind different antigens. Such molecules can be

U.S. Patent No. 4,676,980 (the disclosure of which is incorporated herein by reference in its entirety); Holliger et al., (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; *Whitlow et al.*, (1994) *Protein Eng.* 7:1017-1026 and U.S. Pat. No. 6,121,424.

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produced by techniques known in the art, for example using methods described in Segal,

Humanized antibodies are antibody molecules from non-human species having one or more complementarity determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule. (See, e.g., Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better et al. (1988) Science 240:1041-1043; Liu et al. (1987) Proc. Natl. Acad. Sci. USA 84:3439-3443; Liu et al. (1987) J. Immunol. 139:3521-3526; Sun et al. (1987) Proc. Natl. Acad. Sci. USA 84:214-218; Nishimura et al. (1987) Cancer Res. 47:999-1005; Wood et al. (1985) Nature 314:446-449; and Shaw et al. (1988) J. Natl. Cancer Inst. 80:1553-1559); Morrison (1985) Science 229:1202-1207; Oi et al. (1986) Bio/Techniques 4:214; U.S. Patent 5,225,539; Jones et al. (1986) Nature 321:552-525; Verhoeyan et al. (1988) Science 239:1534; and Beidler et al. (1988) J. Immunol. 141:4053-4060.

More particularly, humanized antibodies can be produced, for example,
using transgenic mice which are incapable of expressing endogenous immunoglobulin
heavy and light chains genes, but which can express human heavy and light chain genes.
The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*,
all or a portion of a polypeptide corresponding to a marker of the invention. Monoclonal

antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995) *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, *e.g.*, U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

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Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, *e.g.*, a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope (Jespers *et al.*, 1994, *Bio/technology* 12:899-903).

The antibodies of the invention can be isolated after production (e.g., from the blood or serum of the subject) or synthesis and further purified by well-known techniques. For example, IgG antibodies can be purified using protein A chromatography. Antibodies specific for a protein of the invention can be selected or (e.g., partially purified) or purified by, e.g., affinity chromatography. For example, a recombinantly expressed and purified (or partially purified) protein of the invention is produced as described herein, and covalently or non-covalently coupled to a solid support such as, for example, a chromatography column. The column can then be used to affinity purify antibodies specific for the proteins of the invention from a sample containing antibodies directed against a large number of different epitopes, thereby generating a substantially purified antibody composition, i.e., one that is substantially free of contaminating antibodies. By a substantially purified antibody composition is meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those of the desired protein of the invention, and preferably at most 20%, yet more preferably at most 10%, and most preferably at most 5% (by dry weight) of the sample is

WO 02/101075 PCT/US02/18638 - 49 -

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contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein of the invention.

In a preferred embodiment, the substantially purified antibodies of the invention may specifically bind to a signal peptide, a secreted sequence, an extracellular domain, a transmembrane or a cytoplasmic domain or cytoplasmic membrane of a protein of the invention. In a particularly preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a protein of the invention. In a more preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a marker protein.

An antibody directed against a protein of the invention can be used to isolate the protein by standard techniques, such as affinity chromatography or immunoprecipitation. Moreover, such an antibody can be used to detect the marker protein or fragment thereof (e.g., in a cellular lysate or cell supernatant) in order to evaluate the level and pattern of expression of the marker. The antibodies can also be used diagnostically to monitor protein levels in tissues or body fluids (e.g. in a cervicalassociated body fluid) as part of a clinical testing procedure, e.g., to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by the use of an antibody derivative, which comprises an antibody of the invention coupled to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ¹²⁵I, ¹³¹I, ³⁵S or ³H.

Antibodies of the invention may also be used as therapeutic agents in treating cancers. In a preferred embodiment, completely human antibodies of the invention are used for therapeutic treatment of human cancer patients, particularly those having an cervical cancer. In another preferred embodiment, antibodies that bind specifically to a marker protein or fragment thereof are used for therapeutic treatment. Further, such therapeutic antibody may be an antibody derivative or immunotoxin comprising an antibody conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

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The conjugated antibodies of the invention can be used for modifying a given biological response, for the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as ribosome-inhibiting protein (see Better et al., U.S. Patent No. 6,146,631, the disclosure of which is incorporated herein in its entirety), abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha.-interferon, beta.-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophase colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982).

Accordingly, in one aspect, the invention provides substantially purified antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. In various embodiments, the substantially purified antibodies of the invention, or fragments or derivatives thereof, can be human, non-human, chimeric and/or humanized antibodies. In another aspect, the invention provides non-human antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. Such non-human antibodies can be goat, mouse, sheep, horse, chicken, rabbit, or rat antibodies. Alternatively, the non-human antibodies of the invention can be chimeric and/or humanized antibodies. In addition, the non-human antibodies of the invention can be polyclonal antibodies or monoclonal antibodies. In still a further aspect, the invention provides monoclonal antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. The monoclonal antibodies can be human, humanized, chimeric and/or non-human antibodies.

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The invention also provides a kit containing an antibody of the invention conjugated to a detectable substance, and instructions for use. Still another aspect of the invention is a pharmaceutical composition comprising an antibody of the invention. In one embodiment, the pharmaceutical composition comprises an antibody of the invention and a pharmaceutically acceptable carrier.

WO 02/101075 PCT/US02/18638 - 52 -

III. Recombinant Expression Vectors and Host Cells

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Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a marker protein (or a portion of such a protein). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, namely expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids (vectors). However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (e.g., in an in vitro transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, Methods in Enzymology: Gene Expression Technology vol.185, Academic Press, San Diego, CA (1991). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and

those which direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

The recombinant expression vectors of the invention can be designed for expression of a marker protein or a segment thereof in prokaryotic (e.g., E. coli) or eukaryotic cells (e.g., insect cells {using baculovirus expression vectors}, yeast cells or mammalian cells). Suitable host cells are discussed further in Goeddel, supra. Alternatively, the recombinant expression vector can be transcribed and translated in vitro, for example using T7 promoter regulatory sequences and T7 polymerase.

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Expression of proteins in prokaryotes is most often carried out in E. coli with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988, Gene 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann *et al.*, 1988, *Gene* 69:301-315) and pET 11d (Studier *et al.*, p. 60-89, In *Gene Expression Technology: Methods in Enzymology* vol.185, Academic Press, San Diego, CA, 1991). Target gene expression from the pTrc vector relies on host RNA

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polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a co-expressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident prophage harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, p. 119-128, In *Gene Expression Technology: Methods in Enzymology* vol. 185, Academic Press, San Diego, CA, 1990. Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada *et al.*, 1992, *Nucleic Acids Res.* 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the expression vector is a yeast expression vector. Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1 (Baldari *et al.*, 1987, *EMBO J.* 6:229-234), pMFa (Kurjan and Herskowitz, 1982, *Cell* 30:933-943), pJRY88 (Schultz *et al.*, 1987, *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, CA), and pPicZ (Invitrogen Corp, San Diego, CA).

Alternatively, the expression vector is a baculovirus expression vector. Baculovirus vectors available for expression of proteins in cultured insect cells (*e.g.*, Sf 9 cells) include the pAc series (Smith *et al.*, 1983, *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers, 1989, *Virology* 170:31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987, *Nature* 329:840) and pMT2PC (Kaufman *et al.*, 1987, *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook *et al.*, *supra*.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Tissuespecific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert et al., 1987, Genes Dev. 1:268-277), lymphoid-specific promoters (Calame and Eaton, 1988, Adv. Immunol. 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989, EMBO J. 8:729-733) and immunoglobulins (Banerji et al., 1983, Cell 33:729-740; Queen and Baltimore, 1983, Cell 33:741-748), neuron-specific promoters (e.g., the neurofilament promoter; Byrne and Ruddle, 1989, Proc. Natl. Acad. Sci. USA 86:5473-5477), pancreas-specific promoters (Edlund et al., 1985, Science 230:912-916), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentallyregulated promoters are also encompassed, for example the murine hox promoters (Kessel and Gruss, 1990, Science 249:374-379) and the α-fetoprotein promoter (Camper and Tilghman, 1989, Genes Dev. 3:537-546).

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The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operably linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to the mRNA encoding a polypeptide of the invention. Regulatory sequences operably linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue-specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid, or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub *et al.*, 1986, *Trends in Genetics*, Vol. 1(1).

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic (e.g., E. coli) or eukaryotic cell (e.g., insect cells, yeast or mammalian cells).

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Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (e.g., for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (e.g., cells that have incorporated the selectable marker will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce a marker protein or a segment thereof. Accordingly, the invention further provides methods for producing a marker protein or a segment thereof using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of the invention (into which a recombinant expression vector encoding a marker protein or a segment thereof has been introduced) in a suitable medium such that the is produced. In another embodiment, the method further

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comprises isolating the marker protein or a segment thereof from the medium or the host cell.

The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which a sequences encoding a marker protein or a segment thereof have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous sequences encoding a marker protein of the invention have been introduced into their genome or homologous recombinant animals in which endogenous gene(s) encoding a marker protein have been altered. Such animals are useful for studying the function and/or activity of the marker protein and for identifying and/or evaluating modulators of marker protein. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologous recombinant animal" is a nonhuman animal, preferably a mammal, more preferably a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, e.g., an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing a nucleic acid encoding a marker protein into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the polypeptide of the invention to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No.

4,873,191 and in Hogan, *Manipulating the Mouse Embryo*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of mRNA encoding the transgene in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying the transgene can further be bred to other transgenic animals carrying other transgenes.

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To create an homologous recombinant animal, a vector is prepared which contains at least a portion of a gene encoding a marker protein into which a deletion, addition or substitution has been introduced to thereby alter, e.g., functionally disrupt, the gene. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous gene is functionally disrupted (i.e., no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous gene is mutated or otherwise altered but still encodes functional protein (e.g., the upstream regulatory region can be altered to thereby alter the expression of the endogenous protein). In the homologous recombination vector, the altered portion of the gene is flanked at its 5' and 3' ends by additional nucleic acid of the gene to allow for homologous recombination to occur between the exogenous gene carried by the vector and an endogenous gene in an embryonic stem cell. The additional flanking nucleic acid sequences are of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see, e.g., Thomas and Capecchi, 1987, Cell 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced gene has homologously recombined with the endogenous gene are selected (see, e.g., Li et al., 1992, Cell 69:915). The selected cells are then injected into a blastocyst of an animal (e.g., a mouse) to form aggregation chimeras (see, e.g., Bradley, Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, Robertson, Ed., IRL, Oxford, 1987, pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed

animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley (1991) *Current Opinion in Bio/Technology* 2:823-829 and in PCT Publication NOS. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169.

In another embodiment, transgenic non-human animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, *e.g.*, Lakso *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.*, 1991, *Science* 251:1351-1355). If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, *e.g.*, by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut *et al.* (1997) *Nature* 385:810-813 and PCT Publication NOS. WO 97/07668 and WO 97/07669.

IV. Pharmaceutical Compositions

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The nucleic acid molecules, polypeptides, and antibodies (also referred to herein as "active compounds") of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is

contemplated. Supplementary active compounds can also be incorporated into the compositions.

The invention includes methods for preparing pharmaceutical compositions for modulating the expression or activity of a marker nucleic acid or protein . Such methods comprise formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein. Such compositions can further include additional active agents. Thus, the invention further includes methods for preparing a pharmaceutical composition by formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein and one or more additional active compounds.

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The invention also provides methods (also referred to herein as "screening assays") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, peptoids, small molecules or other drugs) which (a) bind to the marker, or (b) have a modulatory (*e.g.*, stimulatory or inhibitory) effect on the activity of the marker or, more specifically, (c) have a modulatory effect on the interactions of the marker with one or more of its natural substrates (*e.g.*, peptide, protein, hormone, co-factor, or nucleic acid), or (d) have a modulatory effect on the expression of the marker. Such assays typically comprise a reaction between the marker and one or more assay components. The other components may be either the test compound itself, or a combination of test compound and a natural binding partner of the marker.

The test compounds of the present invention may be obtained from any available source, including systematic libraries of natural and/or synthetic compounds.

Test compounds may also be obtained by any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; see, e.g., Zuckermann et al., 1994, J. Med. Chem.

37:2678-85); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while

the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) Proc. Natl. Acad. Sci. U.S.A. 90:6909; Erb et al. (1994) Proc. Natl. Acad. Sci. USA 91:11422; Zuckermann et al. (1994). J. Med. Chem. 37:2678; Cho et al. (1993) Science 261:1303; Carrell et al. (1994) Angew. Chem. Int. Ed. Engl. 33:2059; Carell et al. (1994) Angew. Chem. Int. Ed. Engl. 33:2061; and in Gallop et al. (1994) J. Med. Chem. 37:1233.

Libraries of compounds may be presented in solution (*e.g.*, Houghten, 1992, *Biotechniques* 13:412-421), or on beads (Lam, 1991, *Nature* 354:82-84), chips (Fodor, 1993, *Nature* 364:555-556), bacteria and/or spores, (Ladner, USP 5,223,409), plasmids (Cull *et al*, 1992, *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith, 1990, *Science* 249:386-390; Devlin, 1990, *Science* 249:404-406; Cwirla *et al*, 1990, *Proc. Natl. Acad. Sci.* 87:6378-6382; Felici, 1991, *J. Mol. Biol.* 222:301-310; Ladner, *supra.*).

In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a protein encoded by or corresponding to a marker or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to a protein encoded by or corresponding to a marker or biologically active portion thereof. Determining the ability of the test compound to directly bind to a protein can be accomplished, for example, by coupling the compound with a radioisotope or enzymatic label such that binding of the compound to the marker can be determined by detecting the labeled marker compound in a complex. For example, compounds (*e.g.*, marker substrates) can be labeled with ¹²⁵I, ³⁵S, ¹⁴C, or ³H, either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, assay components can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

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In another embodiment, the invention provides assays for screening candidate or test compounds which modulate the expression of a marker or the activity of a protein encoded by or corresponding to a marker, or a biologically active portion 5

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thereof. In all likelihood, the protein encoded by or corresponding to the marker can, *in vivo*, interact with one or more molecules, such as but not limited to, peptides, proteins, hormones, cofactors and nucleic acids. For the purposes of this discussion, such cellular and extracellular molecules are referred to herein as "binding partners" or marker "substrate".

One necessary embodiment of the invention in order to facilitate such screening is the use of a protein encoded by or corresponding to marker to identify the protein's natural *in vivo* binding partners. There are many ways to accomplish this which are known to one skilled in the art. One example is the use of the marker protein as "bait protein" in a two-hybrid assay or three-hybrid assay (see, *e.g.*, U.S. Patent No. 5,283,317; Zervos *et al*, 1993, *Cell* 72:223-232; Madura *et al*, 1993, *J. Biol. Chem.* 268:12046-12054; Bartel *et al*,1993, *Biotechniques* 14:920-924; Iwabuchi *et al*, 1993 *Oncogene* 8:1693-1696; Brent WO94/10300) in order to identify other proteins which bind to or interact with the marker (binding partners) and, therefore, are possibly involved in the natural function of the marker. Such marker binding partners are also likely to be involved in the propagation of signals by the marker protein or downstream elements of a marker protein-mediated signaling pathway. Alternatively, such marker protein binding partners may also be found to be inhibitors of the marker protein.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that encodes a marker protein fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming a marker-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be readily detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the marker protein.

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In a further embodiment, assays may be devised through the use of the invention for the purpose of identifying compounds which modulate (e.g., affect either positively or negatively) interactions between a marker protein and its substrates and/or binding partners. Such compounds can include, but are not limited to, molecules such as antibodies, peptides, hormones, oligonucleotides, nucleic acids, and analogs thereof. Such compounds may also be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. The preferred assay components for use in this embodiment is an cervical cancer marker protein identified herein, the known binding partner and/or substrate of same, and the test compound. Test compounds can be supplied from any source.

The basic principle of the assay systems used to identify compounds that interfere with the interaction between the marker protein and its binding partner involves preparing a reaction mixture containing the marker protein and its binding partner under conditions and for a time sufficient to allow the two products to interact and bind, thus forming a complex. In order to test an agent for inhibitory activity, the reaction mixture is prepared in the presence and absence of the test compound. The test compound can be initially included in the reaction mixture, or can be added at a time subsequent to the addition of the marker protein and its binding partner. Control reaction mixtures are incubated without the test compound or with a placebo. The formation of any complexes between the marker protein and its binding partner is then detected. The formation of a complex in the control reaction, but less or no such formation in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the marker protein and its binding partner. Conversely, the formation of more complex in the presence of compound than in the control reaction indicates that the compound may enhance interaction of the marker protein and its binding partner.

The assay for compounds that interfere with the interaction of the marker protein with its binding partner may be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring either the marker protein or its binding partner onto a solid phase and detecting complexes anchored to the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested. For example, test compounds

that interfere with the interaction between the marker proteins and the binding partners (e.g., by competition) can be identified by conducting the reaction in the presence of the test substance, i.e., by adding the test substance to the reaction mixture prior to or simultaneously with the marker and its interactive binding partner. Alternatively, test compounds that disrupt preformed complexes, e.g., compounds with higher binding constants that displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are briefly described below.

In a heterogeneous assay system, either the marker protein or its binding partner is anchored onto a solid surface or matrix, while the other corresponding non-anchored component may be labeled, either directly or indirectly. In practice, microtitre plates are often utilized for this approach. The anchored species can be immobilized by a number of methods, either non-covalent or covalent, that are typically well known to one who practices the art. Non-covalent attachment can often be accomplished simply by coating the solid surface with a solution of the marker protein or its binding partner and drying. Alternatively, an immobilized antibody specific for the assay component to be anchored can be used for this purpose. Such surfaces can often be prepared in advance and stored.

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In related embodiments, a fusion protein can be provided which adds a domain that allows one or both of the assay components to be anchored to a matrix. For example, glutathione-S-transferase/marker fusion proteins or glutathione-S-transferase/binding partner can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, which are then combined with the test compound or the test compound and either the non-adsorbed marker or its binding partner, and the mixture incubated under conditions conducive to complex formation (*e.g.*, physiological conditions). Following incubation, the beads or microtiter plate wells are washed to remove any unbound assay components, the immobilized complex assessed either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of marker binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a marker protein or a marker protein binding partner can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated marker protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the protein-immobilized surfaces can be prepared in advance and stored.

In order to conduct the assay, the corresponding partner of the immobilized assay component is exposed to the coated surface with or without the test compound. After the reaction is complete, unreacted assay components are removed (e.g., by washing) and any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the non-immobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the non-immobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; e.g., using a labeled antibody specific for the initially non-immobilized species (the antibody, in turn, can be directly labeled or indirectly labeled with, e.g., a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which modulate (inhibit or enhance) complex formation or which disrupt preformed complexes can be detected.

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In an alternate embodiment of the invention, a homogeneous assay may be used. This is typically a reaction, analogous to those mentioned above, which is conducted in a liquid phase in the presence or absence of the test compound. The formed complexes are then separated from unreacted components, and the amount of complex formed is determined. As mentioned for heterogeneous assay systems, the order of addition of reactants to the liquid phase can yield information about which test compounds modulate (inhibit or enhance) complex formation and which disrupt preformed complexes.

In such a homogeneous assay, the reaction products may be separated from unreacted assay components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, complexes of molecules may be separated from uncomplexed molecules through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., *Trends Biochem Sci* 1993

Aug;18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the complex as compared to the uncomplexed molecules may be exploited to differentially separate the complex from the remaining individual reactants, for example through the use of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, e.g., Heegaard, 1998, J Mol. Recognit. 11:141-148; Hage and Tweed, 1997, J. Chromatogr. B. Biomed. Sci. Appl., 699:499-525). Gel electrophoresis may also be employed to separate complexed molecules from unbound species (see, e.g., Ausubel et al (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, nondenaturing gels in the absence of reducing agent are typically preferred, but conditions appropriate to the particular interactants will be well known to one skilled in the art. Immunoprecipitation is another common technique utilized for the isolation of a protein-protein complex from solution (see, e.g., Ausubel et al (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, all proteins binding to an antibody specific to one of the binding molecules are precipitated from solution by conjugating the antibody to a polymer bead that may be readily collected by centrifugation. The bound assay components are released from the beads (through a specific proteolysis event or other technique well known in the art which will not disturb the protein-protein interaction in the complex), and a second immunoprecipitation step is performed, this time utilizing antibodies specific for the correspondingly different interacting assay component. In this manner, only formed complexes should remain attached to the beads. Variations in complex formation in both the presence and the absence of a test compound can be compared, thus offering information about the ability of the compound to modulate interactions between the marker protein and its binding partner.

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Also within the scope of the present invention are methods for direct detection of interactions between the marker protein and its natural binding partner and/or a test compound in a homogeneous or heterogeneous assay system without further sample manipulation. For example, the technique of fluorescence energy transfer may be utilized (see, e.g., Lakowicz et al, U.S. Patent No. 5,631,169; Stavrianopoulos et al, U.S. Patent No. 4,868,103). Generally, this technique involves the addition of a fluorophore label on a first 'donor' molecule (e.g., marker or test compound) such that its emitted fluorescent energy will be absorbed by a fluorescent label on a second, 'acceptor' molecule (e.g., marker or test compound), which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (e.g., using a fluorimeter). A test substance which either enhances or hinders participation of one of the species in the preformed complex will result in the generation of a signal variant to that of background. In this way, test substances that modulate interactions between a marker and its binding partner can be identified in controlled assays.

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In another embodiment, modulators of marker expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of marker mRNA or protein in the cell, is determined. The level of expression of marker mRNA or protein in the presence of the candidate compound is compared to the level of expression of marker mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of marker expression based on this comparison. For example, when expression of marker mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of marker mRNA or protein expression. Conversely, when expression of marker mRNA or protein is less (statistically significantly less) in the presence of the candidate compound

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than in its absence, the candidate compound is identified as an inhibitor of marker mRNA or protein expression. The level of marker mRNA or protein expression in the cells can be determined by methods described herein for detecting marker mRNA or protein.

In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a marker protein can be further confirmed *in vivo*, *e.g.*, in a whole animal model for cellular transformation and/or tumorigenesis.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a marker modulating agent, an antisense marker nucleic acid molecule, a marker-specific antibody, or a marker-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

It is understood that appropriate doses of small molecule agents and protein or polypeptide agents depends upon a number of factors within the knowledge of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of these agents will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner desires the agent to have upon the nucleic acid or polypeptide of the invention. Exemplary doses of a small molecule include milligram or microgram amounts per kilogram of subject or sample weight (e.g. about 1 microgram per kilogram to about 500 milligrams per kilogram, about 1 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram. Exemplary doses of a protein or polypeptide include gram, milligram or microgram amounts per kilogram of subject or sample weight (e.g. about 1 microgram per kilogram to about 5 grams per kilogram, about 50 micrograms per kilogram to about 5 grams per kilogram, about 100 micrograms per kilogram to about 500 milligrams per kilogram, or

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about 1 milligram per kilogram to about 50 milligrams per kilogram). It is furthermore understood that appropriate doses of one of these agents depend upon the potency of the agent with respect to the expression or activity to be modulated. Such appropriate doses can be determined using the assays described herein. When one or more of these agents is to be administered to an animal (e.g. a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher can, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific agent employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration.

Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL (BASF; Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy

WO 02/101075 PCT/US02/18638 - 70 -

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syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (e.g., a polypeptide or antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium, and then incorporating the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed.

Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches, and the like can contain any of the following ingredients, or compounds of a similar nature: a

WO 02/101075 PCT/US02/18638 - 71 -

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binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from a pressurized container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems.

Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid.

Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes having monoclonal antibodies incorporated therein or thereon) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the 5

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subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

For antibodies, the preferred dosage is 0.1 mg/kg to 100 mg/kg of body weight (generally 10 mg/kg to 20 mg/kg). If the antibody is to act in the brain, a dosage of 50 mg/kg to 100 mg/kg is usually appropriate. Generally, partially human antibodies and fully human antibodies have a longer half-life within the human body than other antibodies. Accordingly, lower dosages and less frequent administration is often possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration (e.g., into the cervical epithelium). A method for lipidation of antibodies is described by Cruikshank et al. (1997) J. Acquired Immune Deficiency Syndromes and Human Retrovirology 14:193.

The invention also provides vaccine compositions for the prevention and/or treatment of cervical cancer. The invention provides cervical cancer vaccine compositions in which a protein of a marker of Table 1, or a combination of proteins of the markers of Table 1, are introduced into a subject in order to stimulate an immune response against the cervical cancer. The invention also provides cervical cancer vaccine compositions in which a gene expression construct, which expresses a marker or fragment of a marker identified in Table 1, is introduced into the subject such that a protein or fragment of a protein encoded by a marker of Table 1 is produced by transfected cells in the subject at a higher than normal level and elicits an immune response.

In one embodiment, a cervical cancer vaccine is provided and employed as an immunotherapeutic agent for the prevention of cervical cancer. In another embodiment, a cervical cancer vaccine is provided and employed as an immunotherapeutic agent for the treatment of cervical cancer.

By way of example, a cervical cancer vaccine comprised of the proteins of the markers of Table 1, may be employed for the prevention and/or treatment of cervical cancer in a subject by administering the vaccine by a variety of routes, *e.g.*, intradermally, subcutaneously, or intramuscularly. In addition, the cervical cancer

vaccine can be administered together with adjuvants and/or immunomodulators to boost the activity of the vaccine and the subject's response. In one embodiment, devices and/or compositions containing the vaccine, suitable for sustained or intermittent release could be, implanted in the body or topically applied thereto for the relatively slow release of such materials into the body. The cervical cancer vaccine can be introduced along with immunomodulatory compounds, which can alter the type of immune response produced in order to produce a response which will be more effective in eliminating the cancer.

In another embodiment, a cervical cancer vaccine comprised of an expression construct of the markers of Table 1, may be introduced by injection into muscle or by coating onto microprojectiles and using a device designed for the purpose to fire the projectiles at high speed into the skin. The cells of the subject will then express the protein(s) or fragments of proteins of the markers of Table 1 and induce an immune

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response. In addition, the cervical cancer vaccine may be introduced along with expression constructs for immunomodulatory molecules, such as cytokines, which may increase the immune response or modulate the type of immune response produced in order to produce a response which will be more effective in eliminating the cancer.

The marker nucleic acid molecules can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Patent 5,328,470), or by stereotactic injection (see, e.g., Chen et al., 1994, Proc. Natl. Acad. Sci. USA 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, e.g. retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

WO 02/101075 PCT/US02/18638 - 74 -

V. Predictive Medicine

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The present invention pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trails are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining the level of expression of one or more marker proteins or nucleic acids, in order to determine whether an individual is at risk of developing cervical cancer. Such assays can be used for prognostic or predictive purposes to thereby prophylactically treat an individual prior to the onset of the cancer.

Yet another aspect of the invention pertains to monitoring the influence of agents (e.g., drugs or other compounds administered either to inhibit cervical cancer or to treat or prevent any other disorder {i.e. in order to understand any cervical carcinogenic effects that such treatment may have}) on the expression or activity of a marker of the invention in clinical trials. These and other agents are described in further detail in the following sections.

A. Diagnostic Assays

An exemplary method for detecting the presence or absence of a marker protein or nucleic acid in a biological sample involves obtaining a biological sample (e.g. a cervical-associated body fluid) from a test subject and contacting the biological sample with a compound or an agent capable of detecting the polypeptide or nucleic acid (e.g., mRNA, genomic DNA, or cDNA). The detection methods of the invention can thus be used to detect mRNA, protein, cDNA, or genomic DNA, for example, in a biological sample in vitro as well as in vivo. For example, in vitro techniques for detection of mRNA include Northern hybridizations and in situ hybridizations. In vitro techniques for detection of a marker protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. In vitro techniques for detection of genomic DNA include Southern hybridizations. Furthermore, in vivo techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein or fragment thereof. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

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A general principle of such diagnostic and prognostic assays involves preparing a sample or reaction mixture that may contain a marker, and a probe, under appropriate conditions and for a time sufficient to allow the marker and probe to interact and bind, thus forming a complex that can be removed and/or detected in the reaction mixture. These assays can be conducted in a variety of ways.

For example, one method to conduct such an assay would involve anchoring the marker or probe onto a solid phase support, also referred to as a substrate, and detecting target marker/probe complexes anchored on the solid phase at the end of the reaction. In one embodiment of such a method, a sample from a subject, which is to be assayed for presence and/or concentration of marker, can be anchored onto a carrier or solid phase support. In another embodiment, the reverse situation is possible, in which the probe can be anchored to a solid phase and a sample from a subject can be allowed to react as an unanchored component of the assay.

There are many established methods for anchoring assay components to a solid phase. These include, without limitation, marker or probe molecules which are immobilized through conjugation of biotin and streptavidin. Such biotinylated assay components can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the surfaces with immobilized assay components can be prepared in advance and stored.

Other suitable carriers or solid phase supports for such assays include any material capable of binding the class of molecule to which the marker or probe belongs. Well-known supports or carriers include, but are not limited to, glass, polystyrene, nylon, polypropylene, nylon, polyethylene, dextran, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

In order to conduct assays with the above mentioned approaches, the non-immobilized component is added to the solid phase upon which the second component is anchored. After the reaction is complete, uncomplexed components may be removed (e.g., by washing) under conditions such that any complexes formed will remain immobilized upon the solid phase. The detection of marker/probe complexes anchored to the solid phase can be accomplished in a number of methods outlined herein.

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In a preferred embodiment, the probe, when it is the unanchored assay component, can be labeled for the purpose of detection and readout of the assay, either directly or indirectly, with detectable labels discussed herein and which are well-known to one skilled in the art.

It is also possible to directly detect marker/probe complex formation without further manipulation or labeling of either component (marker or probe), for example by utilizing the technique of fluorescence energy transfer (see, for example, Lakowicz et al., U.S. Patent No. 5,631,169; Stavrianopoulos, et al., U.S. Patent No. 4,868,103). A fluorophore label on the first, 'donor' molecule is selected such that, upon excitation with incident light of appropriate wavelength, its emitted fluorescent energy will be absorbed by a fluorescent label on a second 'acceptor' molecule, which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (e.g., using a fluorimeter).

In another embodiment, determination of the ability of a probe to recognize a marker can be accomplished without labeling either assay component (probe or marker) by utilizing a technology such as real-time Biomolecular Interaction Analysis (BIA) (see, e.g., Sjolander, S. and Urbaniczky, C., 1991, Anal. Chem. 63:2338-2345 and Szabo et al., 1995, Curr. Opin. Struct. Biol. 5:699-705). As used herein, "BIA" or "surface plasmon resonance" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (e.g., BIAcore). Changes in the mass at the binding surface (indicative of a binding event) result in alterations of the refractive index of light near the surface (the optical phenomenon of surface plasmon resonance (SPR)), resulting in a detectable signal which can be used as an indication of real-time reactions between biological molecules.

Alternatively, in another embodiment, analogous diagnostic and prognostic assays can be conducted with marker and probe as solutes in a liquid phase. In such an assay, the complexed marker and probe are separated from uncomplexed components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, marker/probe complexes may be separated from uncomplexed assay components through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., 1993, Trends Biochem Sci. 18(8):284-7). 10 Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively 15 different charge properties of the marker/probe complex as compared to the uncomplexed components may be exploited to differentiate the complex from uncomplexed components, for example through the utilization of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, e.g., Heegaard, N.H., 1998, J. Mol. Recognit. Winter 11(1-6):141-8; Hage, D.S., and Tweed, S.A. J Chromatogr B Biomed Sci Appl 1997 Oct 20 10;699(1-2):499-525). Gel electrophoresis may also be employed to separate complexed assay components from unbound components (see, e.g., Ausubel et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, New York, 1987-1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, 25 non-denaturing gel matrix materials and conditions in the absence of reducing agent are typically preferred. Appropriate conditions to the particular assay and components thereof will be well known to one skilled in the art.

In a particular embodiment, the level of marker mRNA can be
determined both by *in situ* and by *in vitro* formats in a biological sample using methods
known in the art. The term "biological sample" is intended to include tissues, cells,
biological fluids and isolates thereof, isolated from a subject, as well as tissues, cells and
fluids present within a subject. Many expression detection methods use isolated RNA.

For *in vitro* methods, any RNA isolation technique that does not select against the isolation of mRNA can be utilized for the purification of RNA from cervical cells (see, *e.g.*, Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York 1987-1999). Additionally, large numbers of tissue samples can readily be processed using techniques well known to those of skill in the art, such as, for example, the single-step RNA isolation process of Chomczynski (1989, U.S. Patent No. 4,843,155).

The isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain reaction analyses and probe arrays. One preferred diagnostic method for the detection of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to the mRNA encoded by the gene being detected. The nucleic acid probe can be, for example, a full-length cDNA, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to a mRNA or genomic DNA encoding a marker of the present invention. Other suitable probes for use in the diagnostic assays of the invention are described herein. Hybridization of an mRNA with the probe indicates that the marker in question is being expressed.

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In one format, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative format, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in detecting the level of mRNA encoded by the markers of the present invention.

An alternative method for determining the level of mRNA marker in a sample involves the process of nucleic acid amplification, *e.g.*, by rtPCR (the experimental embodiment set forth in Mullis, 1987, U.S. Patent No. 4,683,202), ligase chain reaction (Barany, 1991, *Proc. Natl. Acad. Sci. USA*, 88:189-193), self sustained sequence replication (Guatelli *et al.*, 1990, *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi *et al.*, 1988, *Bio/Technology* 6:1197), rolling circle replication (Lizardi *et al.*, U.S. Patent No. 5,854,033) or any other nucleic acid

WO 02/101075 PCT/US02/18638
- 79 -

amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. As used herein, amplification primers are defined as being a pair of nucleic acid molecules that can anneal to 5' or 3' regions of a gene (plus and minus strands, respectively, or vice-versa) and contain a short region in between. In general, amplification primers are from about 10 to 30 nucleotides in length and flank a region from about 50 to 200 nucleotides in length. Under appropriate conditions and with appropriate reagents, such primers permit the amplification of a nucleic acid molecule comprising the nucleotide sequence flanked by the primers.

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For *in situ* methods, mRNA does not need to be isolated from the cervical cells prior to detection. In such methods, a cell or tissue sample is prepared/processed using known histological methods. The sample is then immobilized on a support, typically a glass slide, and then contacted with a probe that can hybridize to mRNA that encodes the marker.

As an alternative to making determinations based on the absolute expression level of the marker, determinations may be based on the normalized expression level of the marker. Expression levels are normalized by correcting the absolute expression level of a marker by comparing its expression to the expression of a gene that is not a marker, *e.g.*, a housekeeping gene that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin gene, or epithelial cell-specific genes. This normalization allows the comparison of the expression level in one sample, *e.g.*, a patient sample, to another sample, *e.g.*, a noncervical cancer sample, or between samples from different sources.

Alternatively, the expression level can be provided as a relative expression level. To determine a relative expression level of a marker, the level of expression of the marker is determined for 10 or more samples of normal versus cancer cell isolates, preferably 50 or more samples, prior to the determination of the expression level for the sample in question. The mean expression level of each of the genes assayed in the larger number of samples is determined and this is used as a baseline expression level for the marker. The expression level of the marker determined for the test sample (absolute level of expression) is then divided by the mean expression value obtained for that marker. This provides a relative expression level.

Preferably, the samples used in the baseline determination will be from cervical cancer or from non-cervical cancer cells of cervical tissue. The choice of the cell source is dependent on the use of the relative expression level. Using expression found in normal tissues as a mean expression score aids in validating whether the marker assayed is cervical specific (versus normal cells). In addition, as more data is accumulated, the mean expression value can be revised, providing improved relative expression values based on accumulated data. Expression data from cervical cells provides a means for grading the severity of the cervical cancer state.

In another embodiment of the present invention, a marker protein is

detected. A preferred agent for detecting marker protein of the invention is an antibody capable of binding to such a protein or a fragment thereof, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment or derivative thereof (e.g., Fab or F(ab')₂) can be used.

The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with

fluorescently labeled streptavidin.

Proteins from cervical cells can be isolated using techniques that are well known to those of skill in the art. The protein isolation methods employed can, for example, be such as those described in Harlow and Lane (Harlow and Lane, 1988, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York).

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A variety of formats can be employed to determine whether a sample contains a protein that binds to a given antibody. Examples of such formats include, but are not limited to, enzyme immunoassay (EIA), radioimmunoassay (RIA), Western blot analysis and enzyme linked immunoabsorbant assay (ELISA). A skilled artisan can readily adapt known protein/antibody detection methods for use in determining whether cervical cells express a marker of the present invention.

In one format, antibodies, or antibody fragments or derivatives, can be used in methods such as Western blots or immunofluorescence techniques to detect the expressed proteins. In such uses, it is generally preferable to immobilize either the antibody or proteins on a solid support. Suitable solid phase supports or carriers include any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

One skilled in the art will know many other suitable carriers for binding antibody or antigen, and will be able to adapt such support for use with the present invention. For example, protein isolated from cervical cells can be run on a polyacrylamide gel electrophoresis and immobilized onto a solid phase support such as nitrocellulose. The support can then be washed with suitable buffers followed by treatment with the detectably labeled antibody. The solid phase support can then be washed with the buffer a second time to remove unbound antibody. The amount of bound label on the solid support can then be detected by conventional means.

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The invention also encompasses kits for detecting the presence of a marker protein or nucleic acid in a biological sample (e.g., cervical smear). Such kits can be used to determine if a subject is suffering from or is at increased risk of developing cervical cancer. For example, the kit can comprise a labeled compound or agent capable of detecting a marker protein or nucleic acid in a biological sample and means for determining the amount of the protein or mRNA in the sample (e.g., an antibody which binds the protein or a fragment thereof, or an oligonucleotide probe which binds to DNA or mRNA encoding the protein). Kits can also include instructions for interpreting the results obtained using the kit.

For antibody-based kits, the kit can comprise, for example: (1) a first antibody (e.g., attached to a solid support) which binds to a marker protein; and, optionally, (2) a second, different antibody which binds to either the protein or the first antibody and is conjugated to a detectable label.

For oligonucleotide-based kits, the kit can comprise, for example: (1) an oligonucleotide, *e.g.*, a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a marker protein or (2) a pair of primers useful for amplifying a marker nucleic acid molecule. The kit can also comprise, *e.g.*, a buffering agent, a preservative, or a protein stabilizing agent. The kit can further comprise components

necessary for detecting the detectable label (e.g., an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit.

B. Pharmacogenomics

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The markers of the invention are also useful as pharmacogenomic markers. As used herein, a "pharmacogenomic marker" is an objective biochemical marker whose expression level correlates with a specific clinical drug response or susceptibility in a patient (see, e.g., McLeod et al. (1999) Eur. J. Cancer 35(12): 1650-1652). The presence or quantity of the pharmacogenomic marker expression is related to the predicted response of the patient and more particularly the patient's tumor to therapy with a specific drug or class of drugs. By assessing the presence or quantity of the expression of one or more pharmacogenomic markers in a patient, a drug therapy which is most appropriate for the patient, or which is predicted to have a greater degree of success, may be selected. For example, based on the presence or quantity of RNA or protein encoded by specific tumor markers in a patient, a drug or course of treatment may be selected that is optimized for the treatment of the specific tumor likely to be present in the patient. The use of pharmacogenomic markers therefore permits selecting or designing the most appropriate treatment for each cancer patient without trying different drugs or regimes.

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Another aspect of pharmacogenomics deals with genetic conditions that alters the way the body acts on drugs. These pharmacogenetic conditions can occur either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common inherited enzymopathy in which the main clinical complication is hemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (e.g., N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show

exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, a PM will show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the level of expression of a marker of the invention in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a modulator of expression of a marker of the invention.

C. Monitoring Clinical Trials

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Monitoring the influence of agents (e.g., drug compounds) on the level of expression of a marker of the invention can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent to affect marker expression can be monitored in clinical trials of subjects receiving treatment for cervical cancer. In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of one or more selected markers of the invention in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the

level of expression of the marker(s) in the post-administration samples; (v) comparing the level of expression of the marker(s) in the pre-administration sample with the level of expression of the marker(s) in the post-administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased expression of the marker gene(s) during the course of treatment may indicate ineffective dosage and the desirability of increasing the dosage. Conversely, decreased expression of the marker gene(s) may indicate efficacious treatment and no need to change dosage.

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D. Electronic Apparatus Readable Media and Arrays

Electronic apparatus readable media comprising a marker of the present invention is also provided. As used herein, "electronic apparatus readable media" refers to any suitable medium for storing, holding or containing data or information that can be read and accessed directly by an electronic apparatus. Such media can include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as compact disc; electronic storage media such as RAM, ROM, EPROM, EEPROM and the like; general hard disks and hybrids of these categories such as magnetic/optical storage media. The medium is adapted or configured for having recorded thereon a marker of the present invention.

As used herein, the term "electronic apparatus" is intended to include any suitable computing or processing apparatus or other device configured or adapted for storing data or information. Examples of electronic apparatus suitable for use with the present invention include stand-alone computing apparatus; networks, including a local area network (LAN), a wide area network (WAN) Internet, Intranet, and Extranet; electronic appliances such as a personal digital assistants (PDAs), cellular phone, pager and the like; and local and distributed processing systems.

As used herein, "recorded" refers to a process for storing or encoding information on the electronic apparatus readable medium. Those skilled in the art can readily adopt any of the presently known methods for recording information on known media to generate manufactures comprising the markers of the present invention.

A variety of software programs and formats can be used to store the marker information of the present invention on the electronic apparatus readable medium. For example, the marker nucleic acid sequence can be represented in a word

WO 02/101075 PCT/US02/18638 - 85 -

processing text file, formatted in commercially-available software such as WordPerfect and MicroSoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like, as well as in other forms. Any number of data processor structuring formats (*e.g.*, text file or database) may be employed in order to obtain or create a medium having recorded thereon the markers of the present invention.

By providing the markers of the invention in readable form, one can routinely access the marker sequence information for a variety of purposes. For example, one skilled in the art can use the nucleotide or amino acid sequences of the present invention in readable form to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of the sequences of the invention which match a particular target sequence or target motif.

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The present invention therefore provides a medium for holding instructions for performing a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer, wherein the method comprises the steps of determining the presence or absence of a marker and based on the presence or absence of the marker, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer and/or recommending a particular treatment for cervical cancer or pre-cervical cancer condition.

The present invention further provides in an electronic system and/or in a network, a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer associated with a marker wherein the method comprises the steps of determining the presence or absence of the marker, and based on the presence or absence of the marker, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer, and/or recommending a particular treatment for the cervical cancer or pre-cervical cancer condition. The method may further comprise the step of receiving phenotypic information associated with the subject and/or acquiring from a network phenotypic information associated with the subject.

The present invention also provides in a network, a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer associated with a marker, said method comprising the steps of receiving information associated with the marker receiving phenotypic information associated with the subject,

acquiring information from the network corresponding to the marker and/or cervical cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has a cervical cancer or a pre-disposition to cervical cancer. The method may further comprise the step of recommending a particular treatment for the cervical cancer or pre-cervical cancer condition.

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The present invention also provides a business method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer, said method comprising the steps of receiving information associated with the marker, receiving phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or cervical cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer. The method may further comprise the step of recommending a particular treatment for the cervical cancer or pre-cervical cancer condition.

The invention also includes an array comprising a marker of the present invention. The array can be used to assay expression of one or more genes in the array. In one embodiment, the array can be used to assay gene expression in a tissue to ascertain tissue specificity of genes in the array. In this manner, up to about 7600 genes can be simultaneously assayed for expression. This allows a profile to be developed showing a battery of genes specifically expressed in one or more tissues.

In addition to such qualitative determination, the invention allows the quantitation of gene expression. Thus, not only tissue specificity, but also the level of expression of a battery of genes in the tissue is ascertainable. Thus, genes can be grouped on the basis of their tissue expression *per se* and level of expression in that tissue. This is useful, for example, in ascertaining the relationship of gene expression between or among tissues. Thus, one tissue can be perturbed and the effect on gene expression in a second tissue can be determined. In this context, the effect of one cell type on another cell type in response to a biological stimulus can be determined. Such a determination is useful, for example, to know the effect of cell-cell interaction at the level of gene expression. If an agent is administered therapeutically to treat one cell type but has an undesirable effect on another cell type, the invention provides an assay to determine the molecular basis of the undesirable effect and thus provides the

opportunity to co-administer a counteracting agent or otherwise treat the undesired effect. Similarly, even within a single cell type, undesirable biological effects can be determined at the molecular level. Thus, the effects of an agent on expression of other than the target gene can be ascertained and counteracted.

In another embodiment, the array can be used to monitor the time course of expression of one or more genes in the array. This can occur in various biological contexts, as disclosed herein, for example development of cervical cancer, progression of cervical cancer, and processes, such a cellular transformation associated with cervical cancer.

The array is also useful for ascertaining the effect of the expression of a gene on the expression of other genes in the same cell or in different cells. This provides, for example, for a selection of alternate molecular targets for therapeutic intervention if the ultimate or downstream target cannot be regulated.

The array is also useful for ascertaining differential expression patterns of one or more genes in normal and abnormal cells. This provides a battery of genes that could serve as a molecular target for diagnosis or therapeutic intervention.

E. Surrogate Markers

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The markers of the invention may serve as surrogate markers for one or more disorders or disease states or for conditions leading up to disease states, and in particular, cervical cancer. As used herein, a "surrogate marker" is an objective biochemical marker which correlates with the absence or presence of a disease or disorder, or with the progression of a disease or disorder (e.g., with the presence or absence of a tumor). The presence or quantity of such markers is independent of the disease. Therefore, these markers may serve to indicate whether a particular course of treatment is effective in lessening a disease state or disorder. Surrogate markers are of particular use when the presence or extent of a disease state or disorder is difficult to assess through standard methodologies (e.g., early stage tumors), or when an assessment of disease progression is desired before a potentially dangerous clinical endpoint is reached (e.g., an assessment of cardiovascular disease may be made using cholesterol levels as a surrogate marker, and an analysis of HIV infection may be made using HIV RNA levels as a surrogate marker, well in advance of the undesirable clinical outcomes of myocardial infarction or fully-developed AIDS). Examples of the use of surrogate

WO 02/101075 PCT/US02/18638 - 88 -

markers in the art include: Koomen et al. (2000) J. Mass. Spectrom. 35: 258-264; and James (1994) AIDS Treatment News Archive 209.

The markers of the invention are also useful as pharmacodynamic markers. As used herein, a "pharmacodynamic marker" is an objective biochemical marker which correlates specifically with drug effects. The presence or quantity of a pharmacodynamic marker is not related to the disease state or disorder for which the drug is being administered; therefore, the presence or quantity of the marker is indicative of the presence or activity of the drug in a subject. For example, a pharmacodynamic marker may be indicative of the concentration of the drug in a biological tissue, in that the marker is either expressed or transcribed or not expressed or transcribed in that tissue in relationship to the level of the drug. In this fashion, the distribution or uptake of the drug may be monitored by the pharmacodynamic marker. Similarly, the presence or quantity of the pharmacodynamic marker may be related to the presence or quantity of the metabolic product of a drug, such that the presence or quantity of the marker is indicative of the relative breakdown rate of the drug in vivo. Pharmacodynamic markers are of particular use in increasing the sensitivity of detection of drug effects, particularly when the drug is administered in low doses. Since even a small amount of a drug may be sufficient to activate multiple rounds of marker transcription or expression, the amplified marker may be in a quantity which is more readily detectable than the drug itself. Also, the marker may be more easily detected due to the nature of the marker itself; for example, using the methods described herein, antibodies may be employed in an immune-based detection system for a protein marker, or marker-specific radiolabeled probes may be used to detect a mRNA marker. Furthermore, the use of a pharmacodynamic marker may offer mechanism-based prediction of risk due to drug treatment beyond the range of possible direct observations. Examples of the use of pharmacodynamic markers in the art include: Matsuda et al. US 6,033,862; Hattis et al. (1991) Env. Health Perspect. 90: 229-238; Schentag (1999) Am. J. Health-Syst. Pharm. 56 Suppl. 3: S21-S24; and Nicolau (1999) Am, J. Health-Syst. Pharm. 56 Suppl. 3: S16-S20.

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VI. Experimental Protocol

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A. Identification of clones

Cervical tumor specific cDNA clones were identified by transcription profiling using mRNA from 12 cervical tumors, 5 CIN III, 5 CIN I and 12 normal cervical tissues. The subtracted libraries were constructed using mRNA from at least three independent normal ectocervix, B-lymphocytes, T-lymphocytes and other white blood cells (in activated and resting states) as drivers and four independent stage 1B cervical tumors or four independent C1N III cervical samples as testers. The top upregulated clones in tumors or C1N III cervical tissues, as determined by proprietary statistical analysis methods, were selected. The clusters in which the selected clones belong were blasted against both public and proprietary sequence databases in order to identify other EST sequences or clusters with significant overlap. Thus, contiguous EST sequences and/or clusters were assembled into full-length genes.

An identification of protein sequence corresponding to the clone was accomplished by obtaining one of the following:

- a) a direct match between the protein sequence and at least one EST sequence in one of its 6 possible translations;
- b) a direct match between the nucleotide sequence for the mRNA corresponding to the protein sequence and at least one EST sequence;
- c) a match between the protein sequence and a contiguous assembly (contig) of the EST sequences with other available EST sequences in the databases in one of its 6 possible translations; or
- d) a match between the nucleotide sequence for the mRNA corresponding to the protein sequence and a contiguous assembly of the EST sequences with other available EST sequences in the databases in one of its 6 possible translations.

VII. Summary of the Data

Tables 1-3 list the markers obtained using the foregoing protocol. The tables provide the name of the gene corresponding to the marker ("Gene Name"), the sequence listing identifier of the cDNA sequence of a nucleotide transcript encoded by or corresponding to the marker ("SEQ ID NO (nts)"), the sequence listing identifier of the amino acid sequence of a protein encoded by the nucleotide transcript ("SEQ ID NO

WO 02/101075 PCT/US02/18638 - 90 -

(AAs)"), and the location of the protein coding sequence within the cDNA sequence ("CDS").

Table 1 lists all of the markers of the invention which are over-expressed in cervical cancer cells compared to normal (*i.e.*, non-cancerous) cervical cells. Table 2 lists newly-identified nucleotide and amino acid sequences useful as cervical cancer markers. Table 3 lists newly-identified nucleotide sequences useful as cervical cancer markers.

Other Embodiments

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims:

What is claimed:

WO 02/101075

- 1. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 143, 145, 147, 149, 151, 167, 203, 217, 231, 233, 51, 65, 67, 68, 100, and 153.
 - 2. A vector which contains the nucleic acid molecule of claim 1.
 - 3. A host cell which contains the nucleic acid molecule of claim 1.

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- 4. A method of assessing whether a patient is afflicted with cervical cancer, the method comprising comparing:
 - a) the level of expression of a marker in a patient sample, wherein the marker is selected from Table 1; and
 - b) the normal level of expression of the marker in a control non-cervical cancer sample,

wherein a significant increase in the level of expression of the marker in the patient sample and the normal level is an indication that the patient is afflicted with cervical cancer.

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- 5. An isolated polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 143, 145, 147, 149, 151, 167, 203, 217, 231, and 233.
- 6. An antibody which selectively binds to the polypeptide of claim 5.
- 7. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 144, 146, 148, 150, 152, 168, 204, 218, 232, and 234.

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8. An antibody which selectively binds to the polypeptide of claim 7.

WO 02/101075 PCT/US02/18638 1

SEQUENCE LISTING

<110> Millennium Pharmaceuticals, Inc. et al. <120> NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF CERVICAL CANCER <130> MRI-035PC <150> US 60/298,159 <151> 2001-06-13 <150> US 60/298.155 <151> 2001-06-13 <150> US 60/335,936 <151> 2001-11-14 <160> 238 <170> FastSEQ for Windows Version 4.0 <210> 1 <211> 12462 <212> DNA <213> Homo sapiens <400> 1 gaagatggcg gcggcggcgg cggtgacggc gcttcccgtg cggctgagga cgatccgcca 60 gtgagcgcgg agactgcttc cacttcgggc gggggagccc cggaccgaat cggctctcta 120 ggccgtggag cttgccgtcc cacctccgtc caaatcgacc tttcctttct atccccaacc 180 accectcaac ceetgtttte ceetgeette ettgeagagg ceatggagga egaggagaga 240 cagaagaagc tggaggccgg caaagccaag cttgcccagt ttcgacaaag aaaagctcag 300 tcggatgggc agagtccttc caagaagcag aaaaaaaaga gaaaaacgtc aagcagtaaa 360 catgatgtgt cagcacacca tgatttgaat attgatcaat cacagtgtaa tgaaatgtac 420 ataaatagtt ctcagagagt agaatcaact gtgattcctg aatctacaat aatgagaact 480 ctacatagtg gagaaataac cagtcatgag cagggettet etgtggaact ggaaagtgaa 540 atttcaacca cagcagatga ctgcagttca gaggtaaatg gttgcagttt tgtgatgaga 600 acaggaaagc ctacaaattt attaagggaa gaagaatttg gtgttgatga ttcttattct 660 gaacaaggag cacaagacag tccgactcat ctagagatga tggaaagtga gttggctggg 720 aaqcaqcatq agattgaaga gctaaacaga gagctggaag aaatgagggt tacctatggg 780 actgaaggac tgcagcagtt acaagaattt gaagctgcca ttaaacaaag agatggcatt 840 ataacccaqc tcactqctaa tttacaacaa qcaaqaaqaq aaaaqqatga gacaatqaqa 900 qaatttttaq aqttqacaqa acaqaqtcaa aaattacaqa ttcaatttca qcaattacaq 960 gctagtgaaa ctctgagaaa cagcactcat agtagcacag ctgcagactt actacaagcc 1020 aaacaacaga tootoactoa toaacagoag ottgaagaac aagaccactt attagaagat 1080 tatcaqaaaa agaaagaaga cttcacaatg caaattagtt tcttgcaaga gaaaattaaa 1140 qtatatqaaa tqqaacaaqa taaaaaaqta qaaaactcaa ataaaqaaga aatacaqqaa 1200 aaqqaqacaa tcattqaaqa attaaacaca aaaataataq aaqaaqaaaa qaaaactctt 1260 gagctaaagg ataaattaac aactgctgat aaattactag gagaattaca agaacagatt 1320 qtqcaaaaqa accaaqaaat aaaaaacatq aaattaqaqc tqactaattc taagcaaaaa 1380 qaaaqacagt cttctgaaga aataaaacag ttaatgggga cagtcgaaga acttcagaag 1440 agaaatcata aagacagcca gttcgaaact gatatagtac aacqaatgga acaagaaaca 1500 caaaqaaagt tagaacaact ccgggcagag ctggatgaga tgtatgggca gcagatagtg 1560

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PCT/US02/18638

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PCT/US02/18638

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WO 02/101075 PCT/US02/18638

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Lys	Gln 450	Glu	Leu	Ile	Arg	Gln 455	His	Met	Ala	Gln	Met 460	Glu	Glu	Met	Lys
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WO 02/101075 PCT/US02/18638

Ser Lys Asn Lys Gln Glu Leu Glu Tyr Lys Ser Lys Leu Lys Ala Leu 885 890 Asn Glu Glu Leu His Leu Gln Arg Ile Asn Pro Thr Thr Val Lys Met 900 905 910 Lys Ser Ser Val Phe Asp Glu Asp Lys Thr Phe Val Ala Glu Thr Leu 920 Glu Met Gly Glu Val Val Glu Lys Asp Thr Thr Glu Leu Met Glu Lys 935 Leu Glu Val Thr Lys Arg Glu Lys Leu Glu Leu Ser Gln Arg Leu Ser 950 955 960 Asp Leu Ser Glu Gln Leu Lys Gln Lys His Gly Glu Ile Ser Phe Leu 965 970 Asn Glu Glu Val Lys Ser Leu Lys Gln Glu Lys Glu Gln Val Ser Leu 980 985 990 Arg Cys Arg Glu Leu Glu Ile Ile Ile Asn His Asn Arg Ala Glu Asn 995 1000 1005 Val Gln Ser Cys Asp Thr Gln Val Ser Ser Leu Leu Asp Gly Val Val 1010 1015 1020 Thr Met Thr Ser Arg Gly Ala Glu Gly Ser Val Ser Lys Val Asn Lys 1025 1030 1035 1040 Ser Phe Gly Glu Glu Ser Lys Ile Met Val Glu Asp Lys Val Ser Phe 1045 1050 1055 Glu Asn Met Thr Val Gly Glu Glu Ser Lys Gln Glu Gln Leu Ile Leu 1060 1065 1070 Asp His Leu Pro Ser Val Thr Lys Glu Ser Ser Leu Arg Ala Thr Gln 1,075 1080 1085 Pro Ser Glu Asn Asp Lys Leu Gln Lys Glu Leu Asn Val Leu Lys Ser 1090 1095 1100 Glu Gln Asn Asp Leu Arg Leu Gln Met Glu Ala Gln Arg Ile Cys Leu 1105 1110 1115 1120 Ser Leu Val Tyr Ser Thr His Val Asp Gln Val Arg Glu Tyr Met Glu 1125 1130 1135 Asn Glu Lys Asp Lys Ala Leu Cys Ser Leu Lys Glu Glu Leu Ile Phe 1140 1145 1150 Ala Gln Glu Glu Lys Ile Lys Glu Leu Gln Lys Ile His Gln Leu Glu 1155 1160 1165 Leu Gln Thr Met Lys Thr Gln Glu Thr Gly Asp Glu Gly Lys Pro Leu 1170 1175 1180 His Leu Leu Ile Gly Lys Leu Gln Lys Ala Val Ser Glu Glu Cys Ser 1185 1190 1195 Tyr Phe Leu Gln Thr Leu Cys Ser Val Leu Gly Glu Tyr Tyr Thr Pro 1205 1210 1215 Ala Leu Lys Cys Glu Val Asn Ala Glu Asp Lys Glu Asn Ser Gly Asp 1220 1225 1230 Tyr Ile Ser Glu Asn Glu Asp Pro Glu Leu Gln Asp Tyr Arg Tyr Glu 1235 1240 1245 Val Gln Asp Phe Gln Glu Asn Met His Thr Leu Leu Asn Lys Val Thr 1255 Glu Glu Tyr Asn Lys Leu Leu Val Leu Gln Thr Arg Leu Ser Lys Ile 1270 1275 Trp Gly Gln Gln Thr Asp Gly Met Lys Leu Glu Phe Gly Glu Glu Asn 1285 1290 1295 Leu Pro Lys Glu Glu Thr Glu Phe Leu Ser Ile His Ser Gln Met Thr 1300 1305 1310 Asn Leu Glu Asp Ile Asp Val Asn His Lys Ser Lys Leu Ser Ser Leu 1315 1320 1325 Gln Asp Leu Glu Lys Thr Lys Leu Glu Glu Gln Val Gln Glu Leu Glu 1330 1335 1340 Ser Leu Ile Ser Ser Leu Gln Gln Gln Leu Lys Glu Thr Glu Gln Asn

1350 1345 1355 Tyr Glu Ala Glu Ile His Cys Leu Gln Lys Arg Leu Gln Ala Val Ser 1365 1370 1375 Glu Ser Thr Val Pro Pro Ser Leu Pro Val Asp Ser Val Val Ile Thr 1380 1385 Glu Ser Asp Ala Gln Arg Thr Met Tyr Pro Gly Ser Cys Val Lys 1395 1400 Asn Ile Asp Gly Thr Ile Glu Phe Ser Gly Glu Phe Gly Val Lys Glu 1410 1415 1420 Glu Thr Asn Ile Val Lys Leu Leu Glu Lys Gln Tyr Gln Glu Gln Leu 1425 1430 1435 1440 Glu Glu Val Ala Lys Val Ile Val Ser Met Ser Ile Ala Phe Ala 1445 1450 1455 Gln Gln Thr Glu Leu Ser Arg Ile Ser Gly Gly Lys Glu Asn Thr Ala 1460 1465 Ser Ser Lys Gln Ala His Ala Val Cys Gln Gln Glu Gln His Tyr Phe 1475 1480 Asn Glu Met Lys Leu Ser Gln Asp Gln Ile Gly Phe Gln Thr Phe Glu 1490 1495 1500 Thr Val Asp Val Lys Phe Lys Glu Glu Phe Lys Pro Leu Ser Lys Glu 1505 1510 1515 1520 Leu Gly Glu His Gly Lys Glu Ile Leu Leu Ser Asn Ser Asp Pro His 1525 1530 1535 Asp Ile Pro Glu Ser Lys Asp Cys Val Leu Thr Ile Ser Glu Glu Met 1540 1545 1550 Phe Ser Lys Asp Lys Thr Phe Ile Val Arg Gln Ser Ile His Asp Glu 1555 1560 1565 Ile Ser Val Ser Ser Met Asp Ala Ser Arg Gln Leu Met Leu Asn Glu 1570 1575 1580 Glu Gln Leu Glu Asp Met Arg Gln Glu Leu Val Arg Gln Tyr Gln Glu 1585 1590 1595 1600 His Gln Gln Ala Thr Glu Leu Leu Arg Gln Ala His Met Arg Gln Met 1605 1610 1615 Glu Arg Gln Arg Glu Asp Gln Glu Gln Leu Gln Glu Glu Ile Lys Arg 1620 1625 1630 Leu Asn Arg Gln Leu Ala Gln Arg Ser Ser Ile Asp Asn Glu Asn Leu 1635 1640 1645 Val Ser Glu Arg Glu Arg Val Leu Leu Glu Glu Leu Glu Ala Leu Lys 1650 1655 1660 Gln Leu Ser Leu Ala Gly Arg Glu Lys Leu Cys Cys Glu Leu Arg Asn 1665 1670 1675 Ser Ser Thr Gln Thr Gln Asn Gly Asn Glu Asn Gln Gly Glu Val Glu 1685 1690 Glu Gln Thr Phe Lys Glu Lys Glu Leu Asp Arg Lys Pro Glu Asp Val 1700 1705 1710 Pro Pro Glu Ile Leu Ser Asn Glu Arg Tyr Ala Leu Gln Lys Ala Asn 1715 1720 1725 Asn Arg Leu Leu Lys Ile Leu Leu Glu Val Val Lys Thr Thr Ala Ala 1730 1735 1740 Val Glu Glu Thr Ile Gly Arg His Val Leu Gly Ile Leu Asp Arg Ser 1745 1750 1755 1760 Ser Lys Ser Gln Ser Ser Ala Ser Leu Ile Trp Arg Ser Glu Ala Glu 1765 1770 1775 Ala Ser Val Lys Ser Cys Val His Glu Glu His Thr Arg Val Thr Asp 1780 1785 1790 Glu Ser Ile Pro Ser Tyr Ser Gly Ser Asp Met Pro Arg Asn Asp Ile 1795 1800 1805 Asn Met Trp Ser Lys Val Thr Glu Glu Gly Thr Glu Leu Ser Gln Arg 1810 1815 1820

Leu Val Arg Ser Gly Phe Ala Gly Thr Glu Ile Asp Pro Glu Asn Glu 1825 1830 1835 1840 Glu Leu Met Leu Asn Ile Ser Ser Arg Leu Gln Ala Ala Val Glu Lys 1845 1850 Leu Glu Ala Ile Ser Glu Thr Ser Ser Gln Leu Glu His Ala Lys 1860 1865 1870 Val Thr Gln Thr Glu Leu Met Arg Glu Ser Phe Arg Gln Lys Gln Glu 1875 1880 1885 Ala Thr Glu Ser Leu Lys Cys Gln Glu Glu Leu Arg Glu Arg Leu His 1890 1895 1900 Glu Glu Ser Arg Ala Arg Glu Gln Leu Ala Val Glu Leu Ser Lys Ala 1905 1910 1915 1920 Glu Gly Val Ile Asp Gly Tyr Ala Asp Glu Lys Thr Leu Phe Glu Arg 1925 1930 1935 Gln Ile Gln Glu Lys Thr Asp Ile Ile Asp Arg Leu Glu Gln Glu Leu 1940 1945 1950 Leu Cys Ala Ser Asn Arg Leu Gln Glu Leu Glu Ala Glu Gln Gln 1955 1960 1965 Ile Gln Glu Glu Arg Glu Leu Leu Ser Arg Gln Lys Glu Ala Met Lys 1970 1975 1980 Ala Glu Ala Gly Pro Val Glu Gln Gln Leu Leu Gln Glu Thr Glu Lys 1985 1990 1995 2000 Leu Met Lys Glu Lys Leu Glu Val Gln Cys Gln Ala Glu Lys Val Arg 2005 2010 2015 Asp Asp Leu Gln Lys Gln Val Lys Ala Leu Glu Ile Asp Val Glu Glu 2020 2025 2030 Gln Val Ser Arg Phe Ile Glu Leu Glu Gln Glu Lys Asn Thr Glu Leu 2035 2040 2045 Met Asp Leu Arg Gln Gln Asn Gln Ala Leu Glu Lys Gln Leu Glu Lys 2050 2055 2060 Met Arg Lys Phe Leu Asp Glu Gln Ala Ile Asp Arg Glu His Glu Arg 2065 2070 2075 2080 Asp Val Phe Gln Gln Glu Ile Gln Lys Leu Glu Gln Gln Leu Lys Val 2085 2090 2095 Val Pro Arg Phe Gln Pro Ile Ser Glu His Gln Thr Arg Glu Val Glu 2100 2105 2110 Gln Leu Ala Asn His Leu Lys Glu Lys Thr Asp Lys Cys Ser Glu Leu 2115 2120 2125 Leu Leu Ser Lys Glu Gln Leu Gln Arg Asp Ile Gln Glu Arg Asn Glu 2130 2135 2140 Glu Ile Glu Lys Leu Glu Phe Arg Val Arg Glu Leu Glu Gln Ala Leu 2145 2150 2155 2160 Leu Val Ser Ala Asp Thr Phe Gln Lys Val Glu Asp Arg Lys His Phe 2165 2170 2175 Gly Ala Val Glu Ala Lys Pro Glu Leu Ser Leu Glu Val Gln Leu Gln 2180 2185 2190 Ala Glu Arg Asp Ala Ile Asp Arg Lys Glu Lys Glu Ile Thr Asn Leu 2195 2200 2205 Glu Glu Gln Leu Glu Gln Phe Arg Glu Glu Leu Glu Asn Lys Asn Glu 2210 2215 2220 Glu Val Gln Gln Leu His Met Gln Leu Glu Ile Gln Lys Lys Glu Ser 2225 2230 2235 Thr Thr Arg Leu Gln Glu Leu Glu Gln Glu Asn Lys Leu Phe Lys Asp 2245 2250 2255 Asp Met Glu Lys Leu Gly Leu Ala Ile Lys Glu Ser Asp Ala Met Ser 2260 2265 2270 Thr Gln Asp Gln His Val Leu Phe Gly Lys Phe Ala Gln Ile Ile Gln 2280 2285 Glu Lys Glu Val Glu Ile Asp Gln Leu Asn Glu Gln Val Thr Lys Leu

2295 2290 2300 Gln Gln Leu Lys Ile Thr Thr Asp Asn Lys Val Ile Glu Glu Lys 2310 2315 2320 Asn Glu Leu Ile Arg Asp Leu Glu Thr Gln Ile Glu Cys Leu Met Ser 2325 2330 2335 Asp Gln Glu Cys Val Lys Arg Asn Arg Glu Glu Glu Ile Glu Gln Leu 2340 2345 Asn Glu Val Ile Glu Lys Leu Gln Gln Glu Leu Ala Asn Ile Gly Gln 2355 2360 Lys Thr Ser Met Asn Ala His Ser Leu Ser Glu Glu Ala Asp Ser Leu 2370 2375 2380 Lys His Gln Leu Asp Val Val Ile Ala Glu Lys Leu Ala Leu Glu Gln 2385 2390 2395 2400 Gln Val Glu Thr Ala Asn Glu Glu Met Thr Phe Met Lys Asn Val Leu 2405 2410 2415 Lys Glu Thr Asn Phe Lys Met Asn Gln Leu Thr Gln Glu Leu Phe Ser 2420 2425 2430 Leu Lys Arg Glu Arg Glu Ser Val Glu Lys Ile Gln Ser Ile Pro Glu 2435 2440 2445 Asn Ser Val Asn Val Ala Ile Asp His Leu Ser Lys Asp Lys Pro Glu 2450 2455 2460 Leu Glu Val Val Leu Thr Glu Asp Ala Leu Lys Ser Leu Glu Asn Gln 2465 2470 2475 2480 Thr Tyr Phe Lys Ser Phe Glu Glu Asn Gly Lys Gly Ser Ile Ile Asn 2485 2490 2495 Leu Glu Thr Arg Leu Leu Gln Leu Glu Ser Thr Val Ser Ala Lys Asp 2500 2505 2510 Leu Glu Leu Thr Gln Cys Tyr Lys Gln Ile Lys Asp Met Gln Glu Gln 2515 2520 2525 Gly Gln Phe Glu Thr Glu Met Leu Gln Lys Lys Ile Val Asn Leu Gln 2530 2535 2540 Lys Ile Val Glu Lys Val Ala Ala Leu Val Ser Gln Ile Gln 2545 2550 2555 Leu Glu Ala Val Gln Glu Tyr Ala Lys Phe Cys Gln Asp Asn Gln Thr 2565 2570 Ile Ser Ser Glu Pro Glu Arg Thr Asn Ile Gln Asn Leu Asn Gln Leu 2580 2585 2590 Arg Glu Asp Glu Leu Gly Ser Asp Ile Ser Ala Leu Thr Leu Arg Ile 2595 2600 2605 Ser Glu Leu Glu Ser Gln Val Val Glu Met His Thr Ser Leu Ile Leu 2610 2615 2620 Glu Lys Glu Gln Val Glu Ile Ala Glu Lys Asn Val Leu Glu Lys Glu 2625 2630 2635 2640 Lys Lys Leu Glu Glu Lys Leu Glu Glu Gly Asn Glu Lys Lys 2645 2650 2655 Gln Arg Glu Lys Glu Lys Lys Arg Ser Pro Gln Asp Val Glu Val Leu 2660 2665 2670 Lys Thr Thr Glu Leu Phe His Ser Asn Glu Glu Ser Gly Phe Phe 2675 2680 2685 Asn Glu Leu Glu Ala Leu Arg Ala Glu Ser Val Ala Thr Lys Ala Glu 2690 2695 2700 Leu Ala Ser Tyr Lys Glu Lys Ala Glu Lys Leu Gln Glu Glu Leu Leu **2705 2710 2715 2720** Val Lys Glu Thr Asn Met Thr Ser Leu Gln Lys Asp Leu Ser Gln Val 2725 2730 2735 Arg Asp His Leu Ala Glu Ala Lys Glu Lys Leu Ser Ile Leu Glu Lys 2740 2745 2750 Glu Asp Glu Thr Glu Val Gln Glu Ser Lys Lys Ala Cys Met Phe Glu 2755 2760 2765

WO 02/101075 PCT/US02/18638

11

Pro Leu Pro Ile 2770	Lys Leu	Ser Lys 2775	Ser	Ile	Ala	Ser 2780		Thr	Asp	Gly
Thr Leu Lys Ile 2785	Ser Ser 279		Gln	Thr	Pro 2795		Ile	Leu	Val	Lys 2800
Asn Ala Gly Ile	Gln Ile 2805	Asn Leu	Gln	Ser 2810		Cys	Ser	Ser	Glu 2815	
Val Thr Glu Ile 282		Gln Phe	Thr 282		Lys	Ile	Glu	Lys 2830		Gln
Glu Leu His Ala 2835	Ala Glu	Ile Leu 284		Met	Glu	Ser	Arg 2845		Ile	Ser
Glu Thr Glu Thr 2850	Leu Lys	Arg Glu 2855	His	Tyr	Val	Ala 2860		Gln	Leu	Leu
Lys Glu Glu Cys 2865	Gly Thr 287		Ala	Val	Ile 2875		Cys	Leu	Arg	Ser 2880
Lys Glu Gly Ser	Ser Ile 2885	Pro Glu	Leu	Ala 2890		Ser	Asp	Ala	Tyr 2895	
Thr Arg Glu Ile 290		Ser Asp	Ser 290!		Ser	Asp	Trp	Gly 2910		Gly
Ile Tyr Leu Thr 2915		292	0	_			2925	5	_	J
Gly Glu Glu Ser 2930	Glu Ser	Ala Thr 2935	Asp	Ser	Phe	Pro 2940	-	Lys	Ile	Lys
Gly Leu Leu Arg 2945	295	0		_	2955	5				2960
Thr Glu Ser Pro	Tyr Ser 2965	Asp Gly	Glu	Asp 2970		Ser	Ile	Gln	Gln 2975	
Ser Glu Pro Trp 298	0	_	298	5	_			2990)	
Ser Leu Lys Asp 2995	Leu Ile	Thr Lys		Gln	Leu	Gln	Arg 3005		Ala	Glu
Val Tyr Asp Ser 3010	Ser Gln			Ser	Phe	Ser 3020	Asp		Arg	Gly
Val Tyr Asp Ser 3010 Glu Leu Leu Leu 3025	Ala Leu 303	Ser His 3015 Gln Gln 0	Glu Val	Phe	Leu 3035	3020 Glu 5	Asp) Glu	Trp Arg	Ser	Val 3040
Val Tyr Asp Ser 3010 Glu Leu Leu Leu 3025 Leu Leu Ala Ala	Ala Leu 303 Phe Arg 3045	Ser His 3015 Gln Gln 0 Thr Glu	Glu Val Leu	Phe Thr 3050	Leu 3035 Ala)	3020 Glu Deu	Asp) Glu Gly	Trp Arg Thr	Ser Thr 3055	Val 3040 Asp
Val Tyr Asp Ser 3010 Glu Leu Leu Leu 3025 Leu Leu Ala Ala Ala Val Gly Leu 306	Ala Leu 303 Phe Arg 3045 Leu Asn	Ser His 3015 Gln Gln O Thr Glu Cys Leu	Glu Val Leu Glu 306	Phe Thr 3050 Gln	Leu 3035 Ala) Arg	3020 Glu D Leu Ile	Asp) Glu Gly Gln	Trp Arg Thr Glu 3070	Ser Thr 3055 Gln	Val 3040 Asp Gly
Val Tyr Asp Ser 3010 Glu Leu Leu Leu 3025 Leu Leu Ala Ala Ala Val Gly Leu 306 Val Glu Tyr Glr 3075	Ala Leu 303 Phe Arg 3045 Leu Asn 00	Ser His 3015 Gln Gln O Thr Glu Cys Leu Met Glu 308	Glu Val Leu Glu 3069 Cys	Phe Thr 3050 Gln 5 Leu	Leu 3035 Ala) Arg Gln	3020 Glu Leu Ile Lys	Asp Glu Gly Gln Ala 3085	Trp Arg Thr Glu 3070 Asp	Ser Thr 3055 Gln) Arg	Val 3040 Asp Gly
Val Tyr Asp Ser 3010 Glu Leu Leu Leu 3025 Leu Leu Ala Ala Ala Val Gly Leu 306 Val Glu Tyr Glr 3075 Ser Leu Leu Ser 3090	Ala Leu 303 Phe Arg 3045 Leu Asn 0 Ala Ala	Ser His 3015 Gln Gln 0 Thr Glu Cys Leu Met Glu 308 Gln Ala 3095	Glu Val Leu Glu 3069 Cys 0 Leu	Phe Thr 3050 Gln Leu His	Leu 3035 Ala) Arg Gln	3020 Glu 5 Leu Ile Lys Gln 3100	Asp Glu Gly Gln Ala 3085 Met	Trp Arg Thr Glu 3070 Asp Asn	Ser Thr 3055 Gln) Arg	Val 3040 Asp Gly Arg
Val Tyr Asp Ser 3010 Glu Leu Leu Leu So25 Leu Leu Ala Ala Ala Val Gly Leu 306 Val Glu Tyr Glr 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105	Ala Leu 303 Phe Arg 3045 Leu Asn 0 Ala Ala Glu Ile Lys Arg 311	Ser His 3015 Gln Gln 0 Thr Glu Cys Leu Met Glu 308 Gln Ala 3095 Glu Gln 0	Glu Val Leu Glu 3069 Cys U Leu Glu	Phe Thr 3050 Gln Leu His	Leu 3035 Ala) Arg Gln Ala Glu 3115	3020 Glu Leu Ile Lys Gln 3100 Lys	Asp) Glu Gly Gln Ala 3085 Met)	Trp Arg Thr Glu 3070 Asp 5 Asn Ser	Thr 3055 Gln) Arg Gly	Val 3040 Asp Gly Arg Arg Glu 3120
Val Tyr Asp Ser 3010 Glu Leu Leu Leu So25 Leu Leu Ala Ala Ala Val Gly Leu 306 Val Glu Tyr Glr 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105 Leu Leu Glu Tyr	Ala Leu 303 Phe Arg 3045 Leu Asn 0 Ala Ala Glu Ile Lys Arg 311 Asn Ile 3125	Ser His 3015 Gln Gln 0 Thr Glu Cys Leu Met Glu 308 Gln Ala 3095 Glu Gln 0 Gln Gln	Glu Val Leu Glu 3069 Cys O Leu Glu Lys	Phe Thr 3050 Gln Leu His Ser Gln 3130	Leu 3035 Ala) Arg Gln Ala Glu 3115 Ser	3020 Glu Leu Ile Lys Gln 3100 Lys Gln	Asp Glu Gly Gln Ala 3085 Met Pro	Trp Arg Thr Glu 3070 Asp Asn Ser Leu	Ser Thr 3055 Gln Arg Gly Gln Glu 3135	Val 3040 Asp Gly Arg Arg Glu 3120 Met
Val Tyr Asp Ser 3010 Glu Leu Leu Leu 3025 Leu Leu Ala Ala Ala Val Gly Leu 306 Val Glu Tyr Glr 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105 Leu Leu Glu Tyr Gln Val Glu Leu 314	Ala Leu 303 Phe Arg 3045 Leu Asn 0 Ala Ala Glu Ile Lys Arg 311 Asn Ile 3125 Ser Ser 0	Ser His 3015 Gln Gln 0 Thr Glu Cys Leu Met Glu 308 Gln Ala 3095 Glu Gln 0 Gln Gln Met Lys	Glu Val Leu Glu 3069 Cys O Leu Glu Lys Asp 3149	Phe Thr 3050 Gln Leu His Ser Gln 3130 Arg	Leu 3035 Ala) Arg Gln Ala Glu 3115 Ser)	3020 Glu Leu Ile Lys Gln 3100 Lys Gln	Asp Glu Gly Gln Ala 3085 Met Pro Met	Trp Arg Thr Glu 3070 Asp 5 Asn Ser Leu Leu 3150	Thr 3055 Gln) Arg Gly Gln Glu 3135 Gln	Val 3040 Asp Gly Arg Arg Glu 3120 Met Glu
Val Tyr Asp Ser 3010 Glu Leu Leu Leu 1013025 Leu Leu Ala Ala Ala Val Gly Leu 306 Val Glu Tyr Glr 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105 Leu Leu Glu Tyr Gln Val Glu Leu 51105 Leu Leu Glu Leu 51105 Gln Val Glu Leu 51155	Ala Leu 303 Phe Arg 3045 Leu Asn O Ala Ala Glu Ile Lys Arg 311 Asn Ile 3125 Ser Ser O Glu Lys	Ser His 3015 Gln Gln 0 Thr Glu Cys Leu Met Glu 308 Gln Ala 3095 Glu Gln 0 Gln Gln Met Lys Met Val 316	Glu Val Leu Glu 3069 Cys 0 Leu Glu Lys Asp 3149 Val 0	Phe Thr 3050 Gln Leu His Ser Gln 3130 Arg	Leu 3035 Ala) Arg Gln Ala Glu 3115 Ser) Ala Glu	3020 Glu Leu Ile Lys Gln 3100 Lys Gln Thr	Asp Glu Gly Gln Ala 3085 Met Pro Met Glu Lys 3165	Trp Arg Thr Glu 3070 Asp Asn Ser Leu Jeu 3150 Ser	Thr 3055 Gln) Arg Gly Glu 3135 Gln)	Val 3040 Asp Gly Arg Arg Glu 3120 Met Glu Leu
Val Tyr Asp Ser 3010 Glu Leu Leu Leu 1013025 Leu Leu Ala Ala Ala Val Gly Leu 306 Val Glu Tyr Glr 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105 Leu Leu Glu Tyr Gln Val Glu Leu 5155 Ala Gln Thr Lys 3170	Ala Leu 303 Phe Arg 3045 Leu Asn 0 Ala Ala Glu Ile Lys Arg 311 Asn Ile 3125 Ser Ser 0 Glu Lys Leu Glu	Ser His 3015 Gln Gln 0 Thr Glu Cys Leu Met Glu 308 Gln Ala 3095 Glu Gln 0 Gln Gln Met Lys Met Val 316 Leu Glu 3175	Glu Val Leu Glu Cys O Leu Glu Lys Asp 3149 Val O Thr	Phe Thr 3050 Gln Leu His Ser Gln 3130 Arg Arg Thr	Leu 3035 Ala) Arg Gln Ala Glu 3115 Ser) Ala Glu Leu	3020 Glu Leu Ile Lys Gln 3100 Lys Gln Thr Leu	Asp Glu Gly Gln Ala 3085 Met Pro Met Glu Lys 3165 Ala	Trp Arg Thr Glu 3070 Asp Asn Ser Leu 3150 Ser Gln	Thr 3055 Gln Arg Gly Gln Glu 3135 Gln His	Val 3040 Asp Gly Arg Arg Glu 3120 Met Glu Leu
Val Tyr Asp Ser 3010 Glu Leu Leu Leu 3025 Leu Leu Ala Ala Ala Val Gly Leu 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105 Leu Leu Glu Tyr Gln Val Glu Leu 314 Gln Leu Ser Ser 3155 Ala Gln Thr Lys 3170 His Leu Lys Glu 3185	Ala Leu 303 Phe Arg 3045 Leu Asn 0 Ala Ala Glu Ile Lys Arg 311 Asn Ile 3125 Ser Ser 0 Glu Lys Leu Glu 319	Ser His 3015 Gln Gln 0 Thr Glu Cys Leu Met Glu 308 Gln Ala 3095 Glu Gln Gln Gln Met Lys Met Val 316 Leu Glu 3175 Ala Phe 0	Glu Val Glu 3069 Cys O Leu Glu Lys Asp 3149 Val O Thr	Phe Thr 3050 Gln 5 Leu His Ser Gln 3130 Arg 5 Ala Thr Leu	Leu 3035 Ala Arg Gln Ala Glu 3115 Ser Ala Glu Leu Glu 3195	3020 Glu Leu Ile Lys Gln 3100 Lys Gln Thr Leu Lys 3180 Val	Asp Glu Gly Gln Ala 3085 Met Pro Met Glu Lys 3165 Ala Lys	Trp Arg Thr Glu 3070 Asp Asn Ser Leu 3150 Ser Gln Asp	Thr 3055 Gln Arg Gly Gln Glu 3135 Gln Glu His	Val 3040 Asp Gly Arg Arg Glu 3120 Met Glu Leu Lys Thr 3200
Val Tyr Asp Ser 3010 Glu Leu Leu Leu 3025 Leu Leu Ala Ala Ala Val Gly Leu 306 Val Glu Tyr Glr 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105 Leu Leu Glu Tyr Gln Val Glu Leu 5155 Ala Gln Thr Lys 3170 His Leu Lys Glu 3185 Asp Glu Val His	Ala Leu 303 Phe Arg 3045 Leu Asn 0 Ala Ala Glu Ile Lys Arg 311 Asn Ile 3125 Ser Ser 0 Glu Lys Leu Glu 1 Leu Glu 319 Leu Leu 3205	Ser His 3015 Gln Gln 0 Thr Glu Cys Leu Met Glu 308 Gln Ala 3095 Glu Gln 0 Gln Gln Met Lys Met Val 316 Leu Glu 3175 Ala Phe 0 Asn Asp	Glu Val Glu 3069 Cys O Leu Glu Lys Asp 3149 Val O Thr Arg	Phe Thr 3050 Gln 5 Leu His Ser Gln 3130 Arg 5 Ala Thr Leu Leu 3210	Leu 3035 Ala Arg Gln Ala Glu 3115 Ser Ala Glu Leu Glu 3195 Ala	3020 Glu Leu Ile Lys Gln 3100 Lys Gln Thr Leu Lys 3180 Val	Asp Glu Gly Gln Ala 3085 Met Pro Met Glu Lys 3165 Ala Lys	Trp Arg Thr Glu 3070 Asp Asn Ser Leu 3150 Ser Gln Asp	Thr 3055 Gln Arg Gly Gln Glu His Lys 3215	Val 3040 Asp Gly Arg Arg Glu 3120 Met Glu Leu Lys Thr 3200 Lys
Val Tyr Asp Ser 3010 Glu Leu Leu Leu 3025 Leu Leu Ala Ala Ala Val Gly Leu 3075 Ser Leu Leu Ser 3090 Lys Ile Thr Leu 3105 Leu Leu Glu Tyr Gln Val Glu Leu 314 Gln Leu Ser Ser 3155 Ala Gln Thr Lys 3170 His Leu Lys Glu 3185	Ala Leu 303 Phe Arg 3045 Leu Asn 0 Ala Ala Glu Ile Lys Arg 311 Asn Ile 3125 Ser Ser 0 Glu Lys Leu Glu 1 Leu Glu 319 Leu Leu 3205 Gln Trp 0	Ser His 3015 Gln Gln 0 Thr Glu Cys Leu Met Glu 308 Gln Ala 3095 Glu Gln Gln Gln Met Lys Met Val 316 Leu Glu 3175 Ala Phe 0 Asn Asp	Glu Val Glu 3069 Cys O Leu Glu Lys Asp 3149 Val O Thr Arg Thr Glu 3229	Phe Thr 3050 Gln Leu His Ser Gln 3130 Arg Arg Ala Thr Leu Leu 3210 Lys	Leu 3035 Ala Arg Gln Ala Glu 3115 Ser Ala Glu Leu Glu 3195 Ala	3020 Glu Leu Ile Lys Gln 3100 Lys Gln Thr Leu Lys 3180 Val Ser	Asp Glu Gly Gln Ala 3085 Met Pro Met Glu Lys 3165 Ala Lys Glu Ala	Trp Arg Thr Glu 3070 Asp Asn Ser Leu 3150 Ser Gln Asp Gln Lys 3230	Thr 3055 Gln Arg Gly Gln Glu 3135 Gln Glu His Lys Lys 3215 Leu	Val 3040 Asp Gly Arg Arg Glu 3120 Met Glu Leu Lys Thr 3200 Lys Gly

WO 02/101075 PCT/US02/18638

		3235	5				3240)				324	5		
Leu	Glu 3250		Gln	Lys	Gln	Arg 3255		Leu	Gln	Leu	Asn 3260		Leu	Leu	Glu
Gln 3265		Lys	Gln	Leu	Leu 3270		Glu	Ser	Gln	Gln 3275		Ile	Glu	Ser	Gln 3280
Arg	Met	Leu	Tyr	Asp 3285		Gln	Leu	Ser	Glu 3290		Gln	Gly	Arg	Asn 329	
Glu	Leu	Gln	Val 3300	Leu)	Leu	Glu	Ser	Glu 3305		Val	Arg	Ile	Arg 331		Met
Ser	Ser	Thr 331		Asp	Arg	Glu	Arg 3320		Leu	His	Ala	Gln 3325		Gln	Ser
Ser	Asp 3330		Thr	Gly	Gln	Ser 3335		Pro	Pro	Leu	Pro 3340		Glu	Asp	Leu
Leu 3345		Glu	Leu	Gln	Lys 3350		Leu	Glu	Glu	Lys 3355		Ser	Arg	Ile	Val 3360
		Leu	Asn	Glu 3365	Thr	-	Lys	Tyr	Lys 3370	Leu		Ser	Leu	Gln 3375	Thr
Arg	Gln	Gln	Met 3380	Glu		Asp	Arg	Gln 3385	Val		Arg	Lys	Thr 339	Leu	
Thr	Glu	Gln 3395		Ala	Asn	Thr	Glu 3400	-	Gln	Lys	Lys	Met 340		Glu	Leu
Gln	Ser 3410		Val	Glu	Asp	Leu 3415		Arg	Gln	Leu	Glu 3420		Lys	Arg	Gln
Gln 3425		Tyr	Lys	Leu	Asp 3430		Glu	Gly	Gln	Arg 3435		Gln	Gly	Ile	Met 3440
Gln	Glu	Phe	Gln	Lys 3445		Glu	Leu	Glu	Arg 3450		Glu	Lys	Arg	Glu 345!	
Arg	Arg	Ile	Leu 3460	Tyr)	Gln	Asn	Leu	Asn 3465		Pro	Thr	Thr	Trp 3470		Leu
Thr	Ser	Asp 3475		Thr	Arg	Asn	Trp 3480		Leu	Gln	Gln	Lys 3485		Glu	Gly
	3490)		Ser		3495	5				3500)			
Gly 3505		Gly	Cys	Asn	His 3510		Leu	Glu	Met	Ile 3515		Gln	Lys	Leu	Gln 3520
Cys	Val	Ala	Ser	Lys 3525		Gln	Val	Leu	Pro 3530		Lys	Ala	Ser	Glu 3535	Arg
Leu	Gln	Phe	Glu 3540	Thr	Ala	Asp	Asp	Glu 3545		Phe	Ile	Trp	Val 3550		Glu
Asn	Ile	Asp 3555		Ile	Ile	Leu	Gln 3560		Gln	Lys	Leu	Thr 3565		Gln	Gln
Gly	Glu 3570		Pro	Ser	Leu	Val 3575		Pro	Ser	Thr	Ser 3580	Cys)	Gly	Ser	Leu
Thr 3585		Arg	Leu	Leu	Arg 3590		Asn	Ala	Glu	Leu 3595		Gly	His	Ile	Ser 3600
Gln	Leu	Thr	Glu	Glu 3605		Asn	Asp	Leu	Arg 3610		Met	Val	Met	Lys 3615	
Glu	Glu	Gln	Ile 3620	Arg	Trp	Tyr	Arg	Gln 3625		Gly	Ala	Gly	Arg 3630	_	Asn
Ser	Ser	Arg 3635		Ser	Leu	Asn	Gly 3640		Ala	Asn	Ile	Glu 3645		Ile	Ile
Ala	Ser 3650		Lys	Glu	Val	Trp 3655		Arg	Glu	Lys	Leu 3660		Leu	Gln	Lys
Ser 3665		Lys	Arg	Ala	Glu 3670		Glu	Val	Tyr	Lys 3675		Lys	Ala	Glu	Leu 3680
		Asp	Ser	Leu 3685	Leu		Thr	Leu	Ser 3690	Pro		Ser	Glu	His 3695	Val
Thr	Leu	Lys	Arg 3700	Ile		Gly	Lys	Tyr 3705	Leu		Ala	Glu	Ser 3710	Phe	

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Glu	Leu	Asn	Ile 500		Leu	Gln	Asp	Thr 505		Ser	Gln	Lys	Glu 510		Leu
Lys	Glu	Glu 515		Gly	Leu	Ile	Leu 520		Glu	Lys	Cys	Ala 525		Gln	Arg
Gln	Leu 530		Asp	Leu	Val	Glu 535		Leu	Ser	Phe	Ser 540		Glu	Gln	Ile
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	His	Lys	Ser	Leu 565		Thr	Val	Glu	Asp 570	Leu	Lys	Ala	Glu	Ile 575	
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Val	Thr	Asn 595	Tyr	Lys	Ile	Lys	Leu 600	Glu	Met	Leu	Glu	Lys 605	Glu	Lys	Asn
Ala	Val 610	Leu	Asp	Arg	Met	Ala 615	Glu	Ser	Gln	Glu	Ala 620	Glu	Leu	Glu	Arg
Leu 625	Arg	Thr	Gln	Leu	Leu 630	Phe	Ser	His	Glu	Glu 635	Glu	Leu	Ser	Lys	Leu 640
Lys	Glu	Asp	Leu	Glu 645	Ile	Glu	His	Arg	Ile 650	Asn	Ile	Glu	Lys	Leu 655	Lys
Asp	Asn	Leu	Gly 660	Ile	His	Tyr	Lys	Gln 665	Gln	Ile	Asp	Gly	Leu 670	Gln	Asn
Glu	Met	Ser 675	Gln	Lys	Ile	Glu	Thr 680	Met	Gln	Phe	Glu	Lys 685	Asp	Asn	Leu
Ile		Lys			Gln					Ile	Ser 700		Leu	Lys	Asp
Leu 705	Gln	Gln	Ser	Leu	Val 710	Asn	Ser	Lys	Ser	Glu 715	Glu	Met	Thr	Leu	Gln 720
Ile	Asn	Glu	Leu	Gln 725	Lys	Glu	Ile	Glu	Ile 730	Leu	Arg	Gln	Glu	Glu 735	Lys
Glu	Lys	Gly	Thr 740	Leu	Glu	Gln	Glu	Val 745	Gln	Glu	Leu	Gln	Leu 750	Lys	Thr
Glu	Leu	Leu 755	Glu	Lys	Gln	Met	Lys 760	Glu	Lys	Glu	Asn	Asp 765	Leu	Gln	Glu
	770					775				Ile	780				
Lys 785	Thr	Leu	Glu	Asp	Met 790	Leu	Lys	Ile	His	Thr 795	Pro	Val	Ser	Gln	Glu 800
Glu	Arg	Leu	Ile	Phe 805	Leu	Asp	Ser	Ile	Lys 810	Ser	Lys	Ser	Lys	Asp 815	Ser
Val	Trp	Glu	Lys 820	Glu	Ile	Glu	Ile	Leu 825	Ile	Glu	Glu	Asn	Glu 830	Asp	Leu
Lys	Gln	Gln	Cys	Ile	Gln	Leu	Asn	Glu	Glu	Ile	Glu	Lys	Gln	Arg	Asn

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Asn Leu Glu Asp Ile Asp Val Asn His Lys Ser Lys Leu Ser Ser Leu 1315 1320 1325 Gln Asp Leu Glu Lys Thr Lys Leu Glu Glu Gln Val Gln Glu Leu Glu 1330 1335 1340 Ser Leu Ile Ser Ser Leu Gln Gln Gln Leu Lys Glu Thr Glu Gln Asn 1345 1350 1355 1360 Tyr Glu Ala Glu Ile His Cys Leu Gln Lys Arg Leu Gln Ala Val Ser 1380 1385 1390 Glu Ser Asp Ala Gln Arg Thr Met Tyr Pro Gly Ser Cys Val Lys 1395 1400 1405 Asn Ile Asp Gly Thr Ile Glu Phe Ser Gly Glu Phe Gly Val Lys Glu 1410 1415 1420 Glu Thr Asn Ile Val Lys Leu Leu Glu Lys Gln Tyr Gln Glu Gln Leu 1430 1435 1440 Glu Glu Val Ala Lys Val Ile Val Ser Met Ser Ile Ala Phe Ala 1445 1450 1455 Gln Gln Thr Glu Leu Ser Arg Ile Ser Gly Gly Lys Glu Asn Thr Ala 1460 1465 1470 Ser Ser Lys Gln Ala His Ala Val Cys Gln Gln Glu Gln His Tyr Phe 1475 1480 1485 Asn Glu Met Lys Leu Ser Gln Asp Gln Ile Gly Phe Gln Thr Phe Glu 1490 1495 1500 Thr Val Asp Val Lys Phe Lys Glu Glu Phe Lys Pro Leu Ser Lys Glu **1510 1515 1520** Leu Gly Glu His Gly Lys Glu Ile Leu Leu Ser Asn Ser Asp Pro His 1525 1530 1535 Asp Ile Pro Glu Ser Lys Asp Cys Val Leu Thr Ile Ser Glu Glu Met 1540 1545 1550 Phe Ser Lys Asp Lys Thr Phe Ile Val Arg Gln Ser Ile His Asp Glu 1555 1560 1565 Ile Ser Val Ser Ser Met Asp Ala Ser Arg Gln Leu Met Leu Asn Glu 1570 1575 1580 Glu Gln Leu Glu Asp Met Arg Gln Glu Leu Val Arg Gln Tyr Gln Glu 1585 1590 1595 His Gln Gln Ala Thr Glu Leu Leu Arg Gln Ala His Met Arg Gln Met 1605 1610 1615 Glu Arg Gln Arg Glu Asp Gln Glu Gln Leu Gln Glu Glu Ile Lys Arg 1620 1625 1630 Leu Asn Arg Gln Leu Ala Gln Arg Ser Ser Ile Asp Asn Glu Asn Leu 1635 1640 1645 Val Ser Glu Arg Glu Arg Val Leu Leu Glu Glu Leu Glu Ala Leu Lys 1650 1655 1660 Gln Leu Ser Leu Ala Gly Arg Glu Lys Leu Cys Cys Glu Leu Arg Asn 1665 1670 1675 1680 Ser Ser Thr Gln Thr Gln Asn Gly Asn Glu Asn Gln Gly Glu Val Glu 1690 1685 Glu Gln Thr Phe Lys Glu Lys Glu Leu Asp Arg Lys Pro Glu Asp Val 1700 1705 Pro Pro Glu Ile Leu Ser Asn Glu Arg Tyr Ala Leu Gln Lys Ala Asn 1720 Asn Arg Leu Leu Lys Ile Leu Leu Glu Val Val Lys Thr Thr Ala Ala 1735 1740 Val Glu Glu Thr Ile Gly Arg His Val Leu Gly Ile Leu Asp Arg Ser 1750 1755 Ser Lys Ser Gln Ser Ser Ala Ser Leu Ile Trp Arg Ser Glu Ala Glu 1765 1770 Ala Ser Val Lys Ser Cys Val His Glu Glu His Thr Arg Val Thr Asp

1	780		1785		17	90	
Glu Ser Ile P 1795	ro Ser Tyr	Ser Gly 180		Met Pro	Arg As 1805	n Asp	Ile
Asn Met Trp S 1810	er Lys Val	Thr Glu 1815	Glu Gly	Thr Glu 182		er Gln	Arg
Leu Val Arg S 1825	er Gly Phe 183	_	Thr Glu	Ile Asp 1835	Pro Gl	u Asn	Glu 1840
Glu Leu Met L	eu Asn Ile 1845	Ser Ser	Arg Leu 185		Ala Va	l Glu 185	
Leu Leu Glu A 1	la Ile Ser 860	Glu Thr	Ser Ser 1865	Gln Leu		s Ala 870	Lys
Val Thr Gln T 1875	hr Glu Leu	Met Arg 188		Phe Arg	Gln Ly 1885	s Gln	Glu
Ala Thr Glu S 1890	er Leu Lys	Cys Gln 1895	Glu Glu	Leu Arg 190		g Leu	His
Glu Glu Ser A 1905	rg Ala Arg 191		Leu Ala	Val Glu 1915	Leu Se	er Lys	Ala 1920
Glu Gly Val I	le Asp Gly 1925	Tyr Ala	Asp Glu 193		Leu Ph	e Glu 193	
Gln Ile Gln G 1	lu Lys Thr 940	Așp Ile	Ile Asp 1945	Arg Leu		n Glu 950	Leu
Leu Cys Ala S 1955		196	0		1965		
Ile Gln Glu G 1970		1975		198	0		
Ala Glu Ala G 1985	ly Pro Val 199		Gln Leu	Leu Gln 1995	Glu Th	ır Glu	Lys 2000
Leu Met Lys G	lu Lys Leu 2005	Glu Val	Gln Cys 201		Glu L	s Val 201	_
Asp Asp Leu G 2	ln Lys Gln 020	Val Lys	Ala Leu 2025	Glu Ile		1 Glu 30	Glu
Gln Val Ser A 2035		204	0		2045		
Met Asp Leu A 2050	rg Gln Gln	Asn Gln 2055	Ala Leu	Glu Lys 206		u Glu	Lys
Met Arg Lys P 2065	he Leu Asp 207		Ala Ile	Asp Arg 2075	Glu Hi	s Glu	Arg 2080
Asp Val Phe G	2085		209	0		209	5
	100		2105		21	10	
Gln Leu Ala A 2115	sn His Leu	Lys Glu 212	Lys Thr O	Asp Lys	Cys Se 2125	r Glu	Leu
Leu Leu Ser L 2130		2135		214	0	_	
Glu Ile Glu L 2145	ys Leu Glu 215		Val Arg	Glu Leu 2155	Glu Gl	n Ala	Leu 2160
Leu Val Glu A	sp Arg Lys 2165	His Phe	Gly Ala 217		Ala Ly	s Pro 217	
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Lys Glu Lys G 2195	lu Ile Thr	Asn Leu 220		Gln Leu	Glu Gl 2205	n Phe	Arg
Glu Glu Leu G 2210	lu Asn Lys	Asn Glu 2215	Glu Val	Gln Gln 222		s Met	Gln
Leu Glu Ile G 2225	ln Lys Lys 223	Glu Ser	Thr Thr			u Leu	Glu 2240
Gln Glu Asn L	ys Leu Phe 2245	Lys Asp	Asp Met 225	Glu Lys	Leu Gl	y Leu 225	Ala

Ile Lys Glu Ser Asp Ala Met Ser Thr Gln Asp Gln His Val Leu Phe 2260 2265 2270 Gly Lys Phe Ala Gln Ile Ile Gln Glu Lys Glu Val Glu Ile Asp Gln 2275 2280 2285 Leu Asn Glu Gln Val Thr Lys Leu Gln Gln Gln Leu Lys Ile Thr Thr 2290 2295 2300 Asp Asn Lys Val Ile Glu Glu Lys Asn Glu Leu Ile Arg Asp Leu Glu 2305 2310 2315 2320 Thr Gln Ile Glu Cys Leu Met Ser Asp Gln Glu Cys Val Lys Arg Asn 2325 2330 2335 Arg Glu Glu Glu Ile Glu Gln Leu Asn Glu Val Ile Glu Lys Leu Gln 2340 2345 2350 Gln Glu Leu Ala Asn Ile Gly Gln Lys Thr Ser Met Asn Ala His Ser 2355 2360 2365 Leu Ser Glu Glu Ala Asp Ser Leu Lys His Gln Leu Asp Val Val Ile 2370 2375 2380 Ala Glu Lys Leu Ala Leu Glu Gln Gln Val Glu Thr Ala Asn Glu Glu 2385 2390 2395 2400 Met Thr Phe Met Lys Asn Val Leu Lys Glu Thr Asn Phe Lys Met Asn 2405 2410 2415 Gln Leu Thr Gln Glu Leu Phe Ser Leu Lys Arg Glu Arg Glu Ser Val 2420 2425 2430 Glu Lys Ile Gln Ser Ile Pro Glu Asn Ser Val Asn Val Ala Ile Asp 2435 2440 2445 His Leu Ser Lys Asp Lys Pro Glu Leu Glu Val Val Leu Thr Glu Asp 2450 2455 2460 Ala Leu Lys Ser Leu Glu Asn Gln Thr Tyr Phe Lys Ser Phe Glu Glu **2465 2470 2475 2480** Asn Gly Lys Gly Ser Ile Ile Asn Leu Glu Thr Arg Leu Leu Gln Leu 2485 2490 2495 Glu Ser Thr Val Ser Ala Lys Asp Leu Glu Leu Thr Gln Cys Tyr Lys 2500 2505 2510 Gln Ile Lys Asp Met Gln Glu Gln Gly Gln Phe Glu Thr Glu Met Leu 2515 2520 2525 Gln Lys Lys Ile Val Asn Leu Gln Lys Ile Val Glu Glu Lys Val Ala 2530 2535 2540 Ala Ala Leu Val Ser Gln Ile Gln Leu Glu Ala Val Gln Glu Tyr Ala 2545 2550 2555 Lys Phe Cys Gln Asp Asn Gln Thr Ile Ser Ser Glu Pro Glu Arg Thr 2565 2570 2575 Asn Ile Gln Asn Leu Asn Gln Leu Arg Glu Asp Glu Leu Gly Ser Asp 2580 2585 2590 Ile Ser Ala Leu Thr Leu Arg Ile Ser Glu Leu Glu Ser Gln Val Val 2595 2600 2605 Glu Met His Thr Ser Leu Ile Leu Glu Lys Glu Gln Val Glu Ile Ala 2610 2615 2620 Glu Lys Asn Val Leu Glu Lys Glu Lys Lys Leu Leu Glu Leu Gln Lys 2630 2635 Leu Leu Glu Gly Asn Glu Lys Lys Gln Arg Glu Lys Glu Lys Arg 2645 2650 2655 Ser Pro Gln Asp Val Glu Val Leu Lys Thr Thr Thr Glu Leu Phe His 2660 2665 Ser Asn Glu Glu Ser Gly Phe Phe Asn Glu Leu Glu Ala Leu Arg Ala 2680 Glu Ser Val Ala Thr Lys Ala Glu Leu Ala Ser Tyr Lys Glu Lys Ala 2695 2690 2700 Glu Lys Leu Gln Glu Glu Leu Leu Val Lys Glu Thr Asn Met Thr Ser 2710 2715 Leu Gln Lys Asp Leu Ser Gln Val Arg Asp His Leu Ala Glu Ala Lys

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25

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WO 02/101075 PCT/US02/18638

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туѕ	rur	ьеи	GTU	ASP	мет	ьeu	глг	Ile	пıs	Inr	rro	vaı	ser	GTD	GLU

WO 02/101075 PCT/US02/18638 31

785 Glu Arg	Ten	Tle	Phe	790	Asn	Ser	Tla	T.v.e	795	T.178	Sar	Tare	Asn	800 Ser
GIU AIG	шец	116	805	пец	ASD	Ser	776	810	Ser	пуз	Ser	пуз	815	per
Val Trp	Glu	Lys 820	Glu	Ile	Glu	Ile	Leu 825	Ile	Glu	Glu	Asn	Glu 830	Asp	Leu
Lys Gln	Gln 835	Cys	Ile	Gln	Leu	Asn 840	Glu	Glu	Ile	Glu	Lys 845	Gln	Arg	Asn
Thr Phe 850					855					860	_			
Gln Glu 865				870					875					880
Ser Lys		_	885				_	890		-		_	895	
Asn Glu		900				_	905					910	_	
Lys Ser	915			_		920					925			
Glu Met 930	_				935	_	_			940				_
Leu Glu 945 Asp Leu			_	950		_			955			_		960
Asp Bed Asn Glu			965					970	_				975	
Arg Cys		980					985					990		
Val Gln	995					1000)				1005	5		
101	0				1015	5				1020	C			
Thr Met 1025				1030)				103	5				1040
Ser Phe			1045	5				1050)				1055	5
Glu Asn		1060	C				1065	5				1070)	
Asp His	ьец 1075		Ser	vaı	Tnr	ьуs 1080		ser	ser	ьеи	1085		Thr	GIN
Pro Ser 109		Asn	Asp	Lys	Leu 1095		Lys	Glu	Leu	Asn 1100		Leu	Lys	Ser
Glu Gln 1105				1110	C				1115	5	_		_	1120
Ser Leu			1125	5				1130)				1135	5
Asn Glu	_	114	o _			_	1145	5	-			1150)	
Ala Gln	115	5				1160)				1165	5		
Leu Gln 117	0				1175	5				1180)			
His Leu 1185				1190)				1195	5			-	1200
Tyr Phe			1205	5				1210	ם כ				1215	5
Ala Leu		122	C				1225	5	_			1230)	_
Tyr Ile	123	5				1240)				1245	5		
Val Gln 125	_	FIIE	GTII	GIU	1255		птѕ	ınr	ьeu	ьец 1260	_	туя	٧dl	T 11T.

Glu Glu Tyr Asn Lys Leu Leu Val Leu Gln Thr Arg Leu Ser Lys Ile 1265 1270 1275 1280
Trp Gly Gln Gln Thr Asp Gly Met Lys Leu Glu Phe Gly Glu Glu Asn

1285 1290 1295

Leu Pro Lys Glu Glu Thr Glu Phe Leu Ser Ile His Ser Gln Met Thr 1300 1305 1310

Asn Leu Glu Asp Ile Asp Val Asn His Lys Ser Lys Leu Ser Ser Leu

1315 1320 1325 Gln Asp Leu Glu Lys Thr Lys Leu Glu Glu Gln Val Gln Glu Leu Glu 1330 1335 1340

Ser Leu Ile Ser Ser Leu Gln Gln Gln Leu Lys Glu Thr Glu Gln Asn 1345 1350 1355 1360

Tyr Glu Ala Glu Ile His Cys Leu Gln Lys Arg Leu Gln Ala Val Ser 1365 1370 1375 Glu Ser Thr Val Pro Pro Ser Leu Pro Val Asp Ser Val Val Ile Thr

1380 1385 1390

Glu Ser Asp Ala Gln Arg Thr Met Tyr Pro Gly Ser Cys Val Lys

1395 1400 1405 Asn Ile Asp Gly Thr Ile Glu Phe Ser Gly Glu Phe Gly Val Lys Glu 1410 1415 1420

Glu Thr Asn Ile Val Lys Leu Leu Glu Lys Gln Tyr Gln Glu Gln Leu 1425 1430 1435 1440

Glu Glu Val Ala Lys Val Ile Val Ser Met Ser Ile Ala Phe Ala

 $1445 \hspace{3em} 1450 \hspace{3em} 1455$ Gln Gln Thr Glu Leu Ser Arg Ile Ser Gly Gly Lys Glu Asn Thr Ala 1460 1465 1470

Ser Ser Lys Gln Ala His Ala Val Cys Gln Gln Glu Gln His Tyr Phe 1475 1480 1485

Asn Glu Met Lys Leu Ser Gln Asp Gln Ile Gly Phe Gln Thr Phe Glu 1490 1495 1500

Thr Val Asp Val Lys Phe Lys Glu Glu Phe Lys Pro Leu Ser Lys Glu 1505 1510 1515 1520

Leu Gly Glu His Gly Lys Glu Ile Leu Leu Ser Asn Ser Asp Pro His 1525 1530 1535

Asp Ile Pro Glu Ser Lys Asp Cys Val Leu Thr Ile Ser Glu Glu Met 1540 1545 1550

Phe Ser Lys Asp Lys Thr Phe Ile Val Arg Gln Ser Ile His Asp Glu 1555 1560 1565

Ile Ser Val Ser Ser Met Asp Ala Ser Arg Gln Leu Met Leu Asn Glu 1570 1575 1580

Glu Gln Leu Glu Asp Met Arg Gln Glu Leu Val Arg Gln Tyr Gln Glu **1585 1590 1595 1600**

His Gln Gln Ala Thr Glu Leu Leu Arg Gln Ala His Met Arg Gln Met 1605 1610 1615

Glu Arg Gln Arg Glu Asp Gln Glu Gln Leu Gln Glu Glu Ile Lys Arg 1620 1625 1630

Leu Asn Arg Gln Leu Ala Gln Arg Ser Ser Ile Asp Asn Glu Asn Leu 1635 1640 1645

Val Ser Glu Arg Glu Arg Val Leu Leu Glu Glu Leu Glu Ala Leu Lys 1650 1655 1660

Gln Leu Ser Leu Ala Gly Arg Glu Lys Leu Cys Cys Glu Leu Arg Asn 1665 1670 1675 1680

Ser Ser Thr Gln Thr Gln Asn Gly Asn Glu Asn Gln Gly Glu Val Glu 1685 1690

Glu Gln Thr Phe Lys Glu Lys Glu Leu Asp Arg Lys Pro Glu Asp Val 1700 1705

Pro Pro Glu Ile Leu Ser Asn Glu Arg Tyr Ala Leu Gln Lys Ala Asn 1720

Asn Arg Leu Leu Lys Ile Leu Leu Glu Val Val Lys Thr Thr Ala Ala

WO 02/101075 PCT/US02/18638 33

1735 1740 Val Glu Glu Thr Ile Gly Arg His Val Leu Gly Ile Leu Asp Arg Ser 1745 1750 1755 Ser Lys Ser Gln Ser Ser Ala Ser Leu Ile Trp Arg Ser Glu Ala Glu 1765 1770 1775 Ala Ser Val Lys Ser Cys Val His Glu Glu His Thr Arg Val Thr Asp 1780 1785 1790 Glu Ser Ile Pro Ser Tyr Ser Gly Ser Asp Met Pro Arg Asn Asp Ile $1795 \\ \text{Asn Met Trp Ser Lys Val Thr Glu Glu Gly Thr Glu Leu Ser Gln Arg} \\$ 1810 1815 1820 Leu Val Arg Ser Gly Phe Ala Gly Thr Glu Ile Asp Pro Glu Asn Glu 1825 1830 1835 1840 Glu Leu Met Leu Asn Ile Ser Ser Arg Leu Gln Ala Ala Val Glu Lys **184**5 **185**0 **185**5 Leu Leu Glu Ala Ile Ser Glu Thr Ser Ser Gln Leu Glu His Ala Lys 1860 1865 1870 Val Thr Gln Thr Glu Leu Met Arg Glu Ser Phe Arg Gln Lys Gln Glu 1875 1880 1885 Ala Thr Glu Ser Leu Lys Cys Gln Glu Glu Leu Arg Glu Arg Leu His 1890 1895 1900 Glu Glu Ser Arg Ala Arg Glu Gln Leu Ala Val Glu Leu Ser Lys Ala 1905 1910 1915 1920 Glu Gly Val Ile Asp Gly Tyr Ala Asp Glu Lys Thr Leu Phe Glu Arg 1925 1930 1935 Gln Ile Gln Glu Lys Thr Asp Ile Ile Asp Arg Leu Glu Gln Glu Leu 1940 1945 1950 Leu Cys Ala Ser Asn Arg Leu Gln Glu Leu Glu Ala Glu Gln Gln Gln 1955 1960 1965 Ile Gln Glu Glu Arg Glu Leu Leu Ser Arg Gln Lys Glu Ala Met Lys 1970 1975 1980 Ala Glu Ala Gly Pro Val Glu Gln Gln Leu Leu Gln Glu Thr Glu Lys 1985 1990 1995 2000 Leu Met Lys Glu Lys Leu Glu Val Gln Cys Gln Ala Glu Lys Val Arg 2005 2010 2015 Asp Asp Leu Gln Lys Gln Val Lys Ala Leu Glu Ile Asp Val Glu Glu 2020 2025 2030 Gln Val Ser Arg Phe Ile Glu Leu Glu Gln Glu Lys Asn Thr Glu Leu 2035 2040 2045 Met Asp Leu Arg Gln Gln Asn Gln Ala Leu Glu Lys Gln Leu Glu Lys 2050 2055 2060 Met Arg Lys Phe Leu Asp Glu Gln Ala Ile Asp Arg Glu His Glu Arg 2065 2070 2075 2080 Asp Val Phe Gln Glu Glu Gln Lys Leu Glu Gln Gln Leu Lys Val 2085 2090 2095 Val Pro Arg Phe Gln Pro Ile Ser Glu His Gln Thr Arg Glu Val Glu 2100 2105 2110 Gln Leu Ala Asn His Leu Lys Glu Lys Thr Asp Lys Cys Ser Glu Leu 2115 2120 2125 Leu Leu Ser Lys Glu Gln Leu Gln Arg Asp Ile Gln Glu Arg Asn Glu 2130 2135 Glu Ile Glu Lys Leu Glu Phe Arg Val Arg Glu Leu Glu Gln Ala Leu 2145 2150 2155 2160 Leu Val Ser Ala Asp Thr Phe Gln Lys Val Glu Asp Arg Lys His Phe 2165 2170 2175 Gly Ala Val Glu Ala Lys Pro Glu Leu Ser Leu Glu Val Gln Leu Gln 2180 2185 2190 Ala Glu Arg Asp Ala Ile Asp Arg Lys Glu Lys Glu Ile Thr Asn Leu 2200

Glu Glu Gln Leu Glu Gln Phe Arg Glu Glu Leu Glu Asn Lys Asn Glu 2210 2215 2220 Glu Val Gln Gln Leu His Met Gln Leu Glu Ile Gln Lys Lys Glu Ser 2230 2235 2240 Thr Thr Arg Leu Glu Glu Leu Glu Glu Asn Lys Leu Phe Lys Asp 2245 2250 2255 Asp Met Glu Lys Leu Gly Leu Ala Ile Lys Glu Ser Asp Ala Met Ser 2260 2265 2270
Thr Gln Asp Gln His Val Leu Phe Gly Lys Phe Ala Gln Ile Ile Gln 2275 2280 2285 Glu Lys Glu Val Glu Ile Asp Gln Leu Asn Glu Gln Val Thr Lys Leu 2290 2295 2300 Gln Gln Leu Lys Ile Thr Thr Asp Asn Lys Val Ile Glu Glu Lys 2310 2315 2320 Asn Glu Leu Ile Arg Asp Leu Glu Thr Gln Ile Glu Cys Leu Met Ser 2325 2330 2335 Asp Gln Glu Cys Val Lys Arg Asn Arg Glu Glu Glu Ile Glu Gln Leu 2340 2345 2350 Asn Glu Val Ile Glu Lys Leu Gln Gln Glu Leu Ala Asn Ile Gly Gln 2355 2360 2365 Lys Thr Ser Met Asn Ala His Ser Leu Ser Glu Glu Ala Asp Ser Leu 2370 . 2375 2380 Lys His Gln Leu Asp Val Val Ile Ala Glu Lys Leu Ala Leu Glu Gln 2385 2390 2395 2400 Gln Val Glu Thr Ala Asn Glu Glu Met Thr Phe Met Lys Asn Val Leu 2405 2410 2415 Lys Glu Thr Asn Phe Lys Met Asn Gln Leu Thr Gln Glu Leu Phe Ser 2420 2425 2430 Leu Lys Arg Glu Arg Glu Ser Val Glu Lys Ile Gln Ser Ile Pro Glu 2435 2440 2445 Asn Ser Val Asn Val Ala Ile Asp His Leu Ser Lys Asp Lys Pro Glu 2450 2455 2460 Leu Glu Val Val Leu Thr Glu Asp Ala Leu Lys Ser Leu Glu Asn Gln 2465 2470 2475 2480 Thr Tyr Phe Lys Ser Phe Glu Glu Asn Gly Lys Gly Ser Ile Ile Asn 2485 2490 2495 Leu Glu Thr Arg Leu Leu Gln Leu Glu Ser Thr Val Ser Ala Lys Asp 2500 2505 2510 Leu Glu Leu Thr Gln Cys Tyr Lys Gln Ile Lys Asp Met Gln Gln Gln 2515 2520 2525 Gly Gln Phe Glu Thr Glu Met Leu Gln Lys Lys Ile Val Asn Leu Gln 2530 2535 2540 Lys Ile Val Glu Glu Lys Val Ala Ala Leu Val Ser Gln Ile Gln Leu Glu Ala Val Gln Glu Tyr Ala Lys Phe Cys Gln Asp Asn Gln Thr 2565 2570 2575 Ile Ser Ser Glu Pro Glu Arg Thr Asn Ile Gln Asn Leu Asn Gln Leu 2580 2585 2590 Arg Glu Asp Glu Leu Gly Ser Asp Ile Ser Ala Leu Thr Leu Arg Ile 2600 2605 Ser Glu Leu Glu Ser Gln Val Val Glu Met His Thr Ser Leu Ile Leu 2615 2620 Glu Lys Glu Gln Val Glu Ile Ala Glu Lys Asn Val Leu Glu Lys Glu 2630 2635 Lys Lys Leu Leu Glu Leu Gln Lys Leu Glu Gly Asn Glu Lys Lys 2645 2650 Gln Arg Glu Lys Glu Lys Lys Arg Ser Pro Gln Asp Val Glu Val Leu 2665 Lys Thr Thr Thr Glu Leu Phe His Ser Asn Glu Glu Ser Gly Phe Phe

2680 Asn Glu Leu Glu Ala Leu Arg Ala Glu Ser Val Ala Thr Lys Ala Glu 2690 2695 2700 Leu Ala Ser Tyr Lys Glu Lys Ala Glu Lys Leu Gln Glu Glu Leu Leu 2705 2710 2715 Val Lys Glu Thr Asn Met Thr Ser Leu Gln Lys Asp Leu Ser Gln Val 2725 2730 2735 Arg Asp His Leu Ala Glu Ala Lys Glu Lys Leu Ser Ile Leu Glu Lys 2740 2745 2750 Glu Asp Glu Thr Glu Val Gln Glu Ser Lys Lys Ala Cys Met Phe Glu 2755 2760 , 2765 Pro Leu Pro Ile Lys Leu Ser Lys Ser Ile Ala Ser Gln Thr Asp Gly 2770 2775 2780 Thr Leu Lys Ile Ser Ser Ser Asn Gln Thr Pro Gln Ile Leu Val Lys 2785 2790 2795 2800 Asn Ala Gly Ile Gln Ile Asn Leu Gln Ser Glu Cys Ser Ser Glu Glu $2805 \hspace{1.5cm} 2810 \hspace{1.5cm} 2815 \\ \mbox{Val Thr Glu Ile Ile Ser Gln Phe Thr Glu Lys Ile Glu Lys Met Gln}$ 2820 2825 2830 Glu Leu His Ala Ala Glu Ile Leu Asp Met Glu Ser Arg His Ile Ser 2835 2840 2845 Glu Thr Glu Thr Leu Lys Arg Glu His Tyr Val Ala Val Gln Leu Leu 2850 2855 2860 Lys Glu Glu Cys Gly Thr Leu Lys Ala Val Ile Gln Cys Leu Arg Ser 2865 2870 2875 2880 Lys Glu Gly Ser Ser Ile Pro Glu Leu Ala His Ser Asp Ala Tyr Gln 2885 2890 2895 Thr Arg Glu Ile Cys Ser Ser Asp Ser Gly Ser Asp Trp Gly Gln Gly 2900 2905 2910 Ile Tyr Leu Thr His Ser Gln Gly Phe Asp Ile Ala Ser Glu Gly Arg 2915 2920 2925 Gly Glu Glu Ser Glu Ser Ala Thr Asp Ser Phe Pro Lys Lys Ile Lys 2930 2935 2940 Gly Leu Leu Arg Ala Val His Asn Glu Gly Met Gln Val Leu Ser Leu 2945 2950 2955 2960 Thr Glu Ser Pro Tyr Ser Asp Gly Glu Asp His Ser Ile Gln Gln Val 2965 2970 2975 Ser Glu Pro Trp Leu Glu Glu Arg Lys Ala Tyr Ile Asn Thr Ile Ser 2980 2985 2990 Ser Leu Lys Asp Leu Ile Thr Lys Met Gln Leu Gln Arg Glu Ala Glu 2995 3000 3005 Val Tyr Asp Ser Ser Gln Ser His Glu Ser Phe Ser Asp Trp Arg Gly 3010 3015 3020 Glu Leu Leu Ala Leu Gln Gln Val Phe Leu Glu Glu Arg Ser Val 3025 3030 3035 3040 Leu Leu Ala Ala Phe Arg Thr Glu Leu Thr Ala Leu Gly Thr Thr Asp 3045 3050 3055 Ala Val Gly Leu Leu Asn Cys Leu Glu Gln Arg Ile Gln Glu Gln Gly 3060 3065 Val Glu Tyr Gln Ala Ala Met Glu Cys Leu Gln Lys Ala Asp Arg Arg 3075 3080 3085 Ser Leu Leu Ser Glu Ile Gln Ala Leu His Ala Gln Met Asn Gly Arg 3090 3095 3100 Lys Ile Thr Leu Lys Arg Glu Glu Glu Ser Glu Lys Pro Ser Gln Glu 3105 3110 3115 3120 Leu Leu Glu Tyr Asn Ile Gln Gln Lys Gln Ser Gln Met Leu Glu Met 3125 3130 3135 Gln Val Glu Leu Ser Ser Met Lys Asp Arg Ala Thr Glu Leu Gln Glu 3145

Gln Leu Ser Ser Glu Lys Met Val Val Ala Glu Leu Lys Ser Glu Leu 3155 3160 3165 Ala Gln Thr Lys Leu Glu Leu Glu Thr Thr Leu Lys Ala Gln His Lys 3170 3175 3180 His Leu Lys Glu Leu Glu Ala Phe Arg Leu Glu Val Lys Asp Lys Thr 3185 3190 3195 3200 Asp Glu Val His Leu Leu Asn Asp Thr Leu Ala Ser Glu Gln Lys Lys 3205 3210 3215 Ser Arg Glu Leu Gln Trp Ala Leu Glu Lys Glu Lys Ala Lys Leu Gly 3220 3225 3230 Arg Ser Glu Glu Arg Asp Lys Glu Glu Leu Glu Asp Leu Lys Phe Ser 3235 3240 3245 Leu Glu Ser Gln Lys Gln Arg Asn Leu Gln Leu Asn Leu Leu Leu Glu 3250 3255 3260 Gln Gln Lys Gln Leu Leu Asn Glu Ser Gln Gln Lys Ile Glu Ser Gln **3265 3270 3275 3280** Arg Met Leu Tyr Asp Ala Gln Leu Ser Glu Glu Gln Gly Arg Asn Leu 3285 3290 3295 Glu Leu Gln Val Leu Leu Glu Ser Glu Lys Val Arg Ile Arg Glu Met 3300 3305 3310 Ser Ser Thr Leu Asp Arg Glu Arg Glu Leu His Ala Gln Leu Gln Ser 3315 3320 3325 Ser Asp Gly Thr Gly Gln Ser Arg Pro Pro Leu Pro Ser Glu Asp Leu 3330 3335 3340 Leu Lys Glu Leu Gln Lys Gln Leu Glu Glu Lys His Ser Arg Ile Val **3345 3350 3355 3360** Glu Leu Leu Asn Glu Thr Glu Lys Tyr Lys Leu Asp Ser Leu Gln Thr 3365 3370 3375 Arg Gln Gln Met Glu Lys Asp Arg Gln Val His Arg Lys Thr Leu Gln 3380 3385 3390 Thr Glu Gln Glu Ala Asn Thr Glu Gly Gln Lys Lys Met His Glu Leu 3395 3400 3405 Gln Ser Lys Val Glu Asp Leu Gln Arg Gln Leu Glu Glu Lys Arg Gln 3410 3415 3420 Gln Val Tyr Lys Leu Asp Leu Glu Gly Gln Arg Leu Gln Gly Ile Met 3425 3430 3435 3440 Gln Glu Phe Gln Lys Gln Glu Leu Glu Arg Glu Glu Lys Arg Glu Ser 3445 3450 3455 Arg Arg Ile Leu Tyr Gln Asn Leu Asn Glu Pro Thr Thr Trp Ser Leu 3460 3465 3470 Thr Ser Asp Arg Thr Arg Asn Trp Val Leu Gln Gln Lys Ile Glu Gly 3475 3480 3485 Glu Thr Lys Glu Ser Asn Tyr Ala Lys Leu Ile Glu Met Asn Gly Gly 3490 3495 3500 Gly Thr Gly Cys Asn His Glu Leu Glu Met Ile Arg Gln Lys Leu Gln 3505 3510 3515 3520 Cys Val Ala Ser Lys Leu Gln Val Leu Pro Gln Lys Ala Ser Glu Arg 3525 3530 3535 Leu Gln Phe Glu Thr Ala Asp Asp Glu Asp Phe Ile Trp Val Gln Glu 3540 3545 3550 Asn Ile Asp Glu Ile Ile Leu Gln Leu Gln Lys Leu Thr Gly Gln Gln 3555 3560 3565 Gly Glu Glu Pro Ser Leu Val Ser Pro Ser Thr Ser Cys Gly Ser Leu 3570 3575 3580 Thr Glu Arg Leu Arg Gln Asn Ala Glu Leu Thr Gly His Ile Ser 3590 3595 Gln Leu Thr Glu Glu Lys Asn Asp Leu Arg Asn Met Val Met Lys Leu 3605 3610 Glu Glu Gln Ile Arg Trp Tyr Arg Gln Thr Gly Ala Gly Arg Asp Asn

3620 3625 3630 Ser Ser Arg Phe Ser Leu Asn Gly Gly Ala Asn Ile Glu Ala Ile Ile 3635 3640 3645

Ala Ser Glu Lys Glu Val Trp Asn Arg Glu Lys Leu Thr Leu Gln Lys 3650 3660

Ser Leu Lys Arg Ala Glu Ala Glu Val Tyr Lys Leu Lys Ala Glu Leu 3665 3670 3675 3680

Arg Asn Asp Ser Leu Leu Gln Thr Leu Ser Pro Asp Ser Glu His Val 3685 3690 3695

Thr Leu Lys Arg Ile Tyr Gly Lys Tyr Leu Arg Ala Glu Ser Phe Arg 3700 3705 3710

Lys Ala Leu Ile Tyr Gln Lys Lys Tyr Leu Leu Leu Leu Gly Gly 3715 3720 3725

Phe Gln Glu Cys Glu Asp Ala Thr Leu Ala Leu Leu Ala Arg Met Gly 3730 3740

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Gly Phe Thr Arg Phe Arg Ser Ala Val Arg Val Ser Ile Ala Ile Ser 3765 3770 3775

Arg Met Lys Phe Leu Val Arg Arg Trp His Arg Val Thr Gly Ser Val 3780 3785 3790

Ser Ile Asn Ile Asn Arg Asp Gly Phe Gly Leu Asn Gln Gly Ala Glu 3795 3800 3805

Lys Thr Asp Ser Phe Tyr His Ser Ser Gly Gly Leu Glu Leu Tyr Gly 3810 3815 3820

Glu Pro Arg His Thr Thr Tyr Arg Ser Arg Ser Asp Leu Asp Tyr Ile 3825 3830 3835 3840

Arg Ser Pro Leu Pro Phe Gln Asn Arg Tyr Pro Gly Thr Pro Ala Asp 3845 3850 3855

Phe Asn Pro Gly Ser Leu Ala Cys Ser Gln Leu Gln Asn Tyr Asp Pro 3860 3865 3870

Asp Arg Ala Leu Thr Asp Tyr Ile Thr Arg Leu Glu Ala Leu Gln Arg 3875 3880 3885

Arg Leu Gly Thr Ile Gln Ser Gly Ala Leu Ser Leu Thr Thr Ser Trp 3890 3895 3900

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WO 02/101075 PCT/US02/18638

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WO 02/101075 PCT/US02/18638

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Pro				Asp	Lys				Glu	Leu				Lys	Ser
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WO 02/101075 PCT/US02/18638 46

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PCT/US02/18638

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<213> Homo sapiens

WO 02/101075 PCT/US02/18638

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<212> PRT

<213> Homo sapiens

<400> 12

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<211> 2298

<212> DNA

<213> Homo sapiens

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<210> 14

<211> 331

<212> PRT

<213> Homo sapiens

<400> 14

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Arg Ala Ile Arg Gln Ala Arg Ala Arg Ala Arg Leu Pro Val Thr Thr
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Trp Arg Ile Ser Ala Gly Ser Gly Gly Gln Ala Glu Arg Thr Ile Ala
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Gly Thr Thr Arg Ala Val Ser Arg Gly Ala Arg Ile Leu Ser Ala Thr
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                                                    270
Thr Ser Gly Ile Phe Leu Ala Leu Asp Val Val Asn Leu Val Tyr Glu
                            280
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Ser Lys His Leu His Glu Gly Ala Lys Ser Ala Ser Ala Glu Glu Leu
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<213> Homo sapiens

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<211> 265

<212> PRT

<213> Homo sapiens

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56

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Gly Gly His Ile Asn Pro Ala Ile Thr Leu Ala Leu Leu Val Gly Asn
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Gln Ile Ser Leu Leu Arg Ala Phe Phe Tyr Val Ala Ala Gln Leu Val
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Gly Ala Ile Ala Gly Ala Gly Ile Leu Tyr Gly Val Ala Pro Leu Asn
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                                                    110
Ala Arg Gly Asn Leu Ala Val Asn Ala Leu Asn Asn Asn Thr Thr Gln
        115
                            120
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Gly Gln Ala Met Val Val Glu Leu Ile Leu Thr Phe Gln Leu Ala Leu
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Cys Ile Phe Ala Ser Thr Asp Ser Arg Arg Thr Ser Pro Val Gly Ser
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                                        155
Pro Ala Leu Ser Ile Gly Leu Ser Val Thr Leu Gly His Leu Val Gly
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                                                        175
Ile Tyr Phe Thr Gly Cys Ser Met Asn Pro Ala Arg Ser Phe Gly Pro
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                                                    190
Ala Val Val Met Asn Arg Phe Ser Pro Ala His Trp Val Phe Trp Val
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                                                205
Gly Pro Ile Val Gly Ala Val Leu Ala Ala Ile Leu Tyr Phe Tyr Leu
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                                            220
Leu Phe Pro Asn Ser Leu Ser Leu Ser Glu Arg Val Ala Ile Ile Lys
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<213> Homo sapiens

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Ile Ile Val Ile Leu Gly Val Pro Leu Ile Ile Phe Thr Ile Lys Ala
Asn Ser Glu Ala Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg
                       55
Asn Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly
                   70
                                       75
Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met
Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys
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<213> Homo sapiens

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Glu Arg Gln Asp Pro Gly Ser Ala Pro Ser Pro Leu Ser Leu Leu His 115 120 Pro Gly Val Ala Ala Lys Gly Lys His Ala Ser Glu Lys Arg His Lys 135 Cys Pro Tyr Ser Gly Cys Gly Lys Val Tyr Gly Lys Ser Ser His Leu 150 155 Lys Ala His Tyr Arg Val His Thr Gly Glu Arg Pro Phe Pro Cys Thr 165 170 Trp Pro Asp Cys Leu Lys Lys Phe Ser Arg Ser Asp Glu Leu Thr Arg 185 180 190 His Tyr Arg Thr His Thr Gly Glu Lys Gln Phe Arg Cys Pro Leu Cys 195 200 205 Glu Lys Arg Phe Met Arg Ser Asp His Leu Thr Lys His Ala Arg Arg 215 220 His Thr Glu Phe His Pro Ser Met Ile Lys Arg Ser Lys Lys Ala Leu 230 235 Ala Asn Ala Leu

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<213> Homo sapiens

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<212> PRT

<213> Homo sapiens

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Leu Tyr Thr Gly Phe Ser Ile Leu Val Thr Leu Leu Leu Ala Gly Gln
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Ala Thr Thr Ala Tyr Phe Leu Tyr Gln Gln Gln Gly Arg Leu Asp Lys
                    70
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Leu Thr Val Thr Ser Gln Asn Leu Gln Leu Glu Asn Leu Arg Met Lys
Leu Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro
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                                                    110
Leu Leu Met Gln Ala Leu Pro Met Gly Ala Leu Pro Gln Gly Pro Met
                            120
                                                125
Gln Asn Ala Thr Lys Tyr Gly Asn Met Thr Glu Asp His Val Met His
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                                            140
Leu Leu Gln Asn Ala Asp Pro Leu Lys Val Tyr Pro Pro Leu Lys Gly
                    150
                                        155
Ser Phe Pro Glu Asn Leu Arg His Leu Lys Asn Thr Met Glu Thr Ile
                                    170
                165
                                                        175
Asp Trp Lys Val Phe Glu Ser Trp Met His His Trp Leu Leu Phe Glu
            180
                                185
Met Ser Arg His Ser Leu Glu Gln Lys Pro Thr Asp Ala Pro Pro Lys
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Glu Ser Leu Glu Leu Glu Asp Pro Ser Ser Gly Leu Gly Val Thr Lys
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Gln Asp Leu Gly Pro Val Pro Met
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<213> Homo sapiens

<400> 26

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Gln Val Cys Ser Ile Leu Trp Ser Pro His Tyr Lys Glu Leu Ile Ser 405 410 Gly His Gly Phe Ala Gln Asn Gln Leu Val Ile Trp Lys Tyr Pro Thr 420 425 Met Ala Lys Val Ala Glu Leu Lys Gly His Thr Ser Arg Val Leu Ser 440 Leu Thr Met Ser Pro Asp Gly Ala Thr Val Ala Ser Ala Ala Asp 455 Glu Thr Leu Arg Leu Trp Arg Cys Phe Glu Leu Asp Pro Ala Arg Arg 470 475 Arg Glu Arg Glu Lys Ala Ser Ala Ala Lys Ser Ser Leu Ile His Gln 490 Gly Ile Arg

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Ala Gln Asn Gly Phe Gly Arg Thr Ala Leu Gln Val Met Lys Leu Gly
                            40
Asn Pro Glu Ile Ala Arg Arg Leu Leu Arg Gly Ala Asn Pro Asp
                        5.5
Leu Lys Asp Arg Thr Gly Phe Ala Val Ile His Asp Ala Ala Arg Ala
                    70
                                        75
Gly Phe Leu Asp Thr Leu Gln Thr Leu Leu Glu Phe Gln Ala Asp Val
                8.5
                                    90
Asn Ile Glu Asp Asn Glu Gly Asn Leu Pro Leu His Leu Ala Ala Lys
                                105
Glu Gly His Leu Arg Val Val Glu Phe Leu Val Lys His Thr Ala Ser
                            120
        115
                                                125
Asn Val Gly His Arg Asn His Lys Gly Asp Thr Ala Cys Asp Leu Ala
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Arg Leu Tyr Gly Arg Asn Glu Val Val Ser Leu Met Gln Ala Asn Gly
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Ala Gly Gly Ala Thr Asn Leu Gln
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<212> DNA
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Ala 385	Gly	Asn	Pro	Gly	Ala 390	Asp	Gly	Gln	Pro	Gly 395	Ala	Lys	Gly	Ala	Asn 400
_			Gly	405					410			_		415	
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Ser	Gly	Glu 435	Pro	Gly	Ala	Pro	Gly 440	Ser	Lys	Gly	Asp	Thr 445	Gly	Ala	Lys
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465		_	Lys	_	470		_	_		475	_			_	480
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			Gly 500					505					510		
		515	Pro				520					525			
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	_	_	Arg Met	565				_	570					575	
	_		580 Gly	_			_	585	_	_			590		
_	_	595	Lys		_	_	600		_			605			_
	610		Ala			615					620				
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_			Glu	645		_			650			_		655	_
_			660 Arg					665					670		
		675	Gly				680					685			
_	690		Ala			695		_			700	_			_
705			Pro		710					715					720
			Gly	725					730					735	
			740 Ser					745					750		
		755	Pro				760					765			
	770		Gly			775					780				
785			Glu		790	_			_	795					800
			Asp	805					810					815	
	_		820 Gly					825					830		
		835	Pro				840					845			_
. 10	ттО	arl	110	± 4.4	OT A	WOII	v Cl T	or A	ura.	110	оту	11± C	-uyo	оту	лта

850 Arg Gly Ser A	Ala Gly Pro	855 Pro Gly	Ala Thr	860 Gly Phe		Ala	Ala
865 Gly Arg Val (870 Gly Pro Pro	Gly Pro	Ser Gly	875 Asn Ala	Gly Pro	Pro	880 Gly
Pro Pro Gly 1	885 Pro Ala Gly	Lys Glu	890 Gly Gly		Pro Arg	895 Gly	Glu
Thr Gly Pro A	900 Ala Gly Arg	Pro Glv	905 Glu Val	Glv Pro	910 Pro Glv	Pro	Pro
915 Gly Pro Ala (920		_	925		
930		935		940			
Ala Pro Gly 5	950			955			960
Val Gly Leu 1	965		970		_	975	
Gly Pro Ser (Gly Glu Pro 980	Gly Lys	Gln Gly 985	Pro Ser	Gly Ala 990	Ser	Gly
Glu Arg Gly 1 995	Pro Pro Gly	Pro Met 100	_	Pro Gly	Leu Ala 1005	Gly	Pro
Pro Gly Glu S 1010	Ser Gly Arg	Glu Gly 1015	Ala Pro	Ala Ala 102	_	Ser	Pro
Gly Arg Asp (Gly Ser Pro 1030		Lys Gly	Asp Arg 1035	Gly Glu	Thr	Gly 1040
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Gly Pro Ala (Gly Pro	Val Gly	Ala Arg			Gly
Pro Gln Gly 1	Pro Arg Gly			Thr Gly	Glu Gln	Gly	Asp
Arg Gly Ile 1	Lys Gly His 1110	Arg Gly	Phe Ser			Pro	Pro 1120
Gly Pro Pro (Gln Gly 113	Pro Ser	Gly Ala	Ser 1135	Gly
Pro Ala Gly		Pro Pro			Ala Pro	Gly	
Asp Gly Leu A		Pro Gly 116	Pro Ile	Gly Pro			Arg
Gly Arg Thr (Gly Asp Ala			Pro Pro 118	Gly Pro	Pro	Gly
Pro Pro Gly 1	Pro Pro Gly 1190	Pro Pro	Ser Ala	Gly Phe		Ser	
Leu Pro Gln I	Pro Pro Gln				Gly Arg		
Arg Ala Asp A		Val Val					
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1235 Glu Gly Ser A	Arg Lys Asn					Lys	Met
1250 Cys His Ser <i>I</i>		_	Glu Tyr	126 Trp Ile		Asn	Gln
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Glu Thr Cys V	1285 Val Tyr Pro	Thr Gln	129 Pro Ser		Gln Lys	1295 Asn	
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1315		132			1325	-	

Ser Met Thr Asp Gly Phe Gln Phe Glu Tyr Gly Gly Gln Gly Ser Asp 1335 Pro Ala Asp Val Ala Ile Gln Leu Thr Phe Leu Arg Leu Met Ser Thr 1350 1355 Glu Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Val Ala Tyr 1365 1370 Met Asp Gln Gln Thr Gly Asn Leu Lys Lys Ala Leu Leu Leu Lys Gly 1385 1390 Ser Asn Glu Ile Glu Ile Arg Ala Glu Gly Asn Ser Arg Phe Thr Tyr 1400 1405 Ser Val Thr Val Asp Gly Cys Thr Ser His Thr Gly Ala Trp Gly Lys 1415 1420 Thr Val Ile Glu Tyr Lys Thr Thr Lys Ser Ser Arg Leu Pro Ile Ile 1425 1430 1435 Asp Val Ala Pro Leu Asp Val Gly Ala Pro Asp Gln Glu Phe Gly Phe 1445 1450 Asp Val Gly Pro Val Cys Phe Leu 1460

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<213> Homo sapiens

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His	Ser	Leu 435	Leu	Ile	Lys	Asn	Leu 440	Lys	Asn	Glu	Ile	Thr 445	Lys	Lys	Val
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		595	Glu -				600					605	_	-	_
	610		Leu			615					620				
11e 625	TTE	Ala	Tyr	Leu	630	гÀг	гйг	GTĀ	Tyr	Pro 635	G⊥u	Val	Ala	Leu	His 640
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			Ile 660					665				_	670		
	_	675	Lys				680					685			
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			Glu	725					730					735	
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	770		Glu			775					780		_		
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Ala	Glu		Gln	Leu	Asp	Glu	Asp	Gly	Phe	Val	Glu	Ala	Thr	Glu	Gly

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Leu Val Leu Asp Gly Cys Gly Cys Cys Arg Val Cys Ala Lys Gln Leu
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Gly Glu Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu
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Phe Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys Thr
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Gly Ala Val Gly Cys Met Pro Leu Cys Ser Met Asp Val Arg Leu Pro
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Ser Pro Asp Cys Pro Phe Pro Arg Arg Val Lys Leu Pro Gly Lys Cys
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Cys Glu Glu Trp Val Cys Asp Glu Pro Lys Asp Gln Thr Val Val Gly
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Pro Ala Leu Ala Ala Tyr Arg Leu Glu Asp Thr Phe Gly Pro Asp Pro
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Cys Ser Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp
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Asn Ala Ser Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg
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Pro Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys
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                                    250
Ile Arg Thr Pro Lys Ile Ser Lys Pro Ile Lys Phe Glu Leu Ser Gly
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Cys Thr Ser Met Lys Thr Tyr Arg Ala Lys Phe Cys Gly Val Cys Thr
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Asp Gly Arg Cys Cys Thr Pro His Arg Thr Thr Thr Leu Pro Val Glu
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Pro Phe Thr Leu Gly Lys Glu Phe Lys Glu Gly His Ser Tyr Tyr
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<211> 5065

<212> PRT

<213> Homo sapiens

<400> 52

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Thr	Phe 210	Arg	Ser	Met	Gly	Gly 215	Ala	Val	Ser	Ala	Ala 220	Glu	Leu	Leu	Glu
Val 225	Gly	Ile	Leu	Asp	Glu 230	Gln	Ala	Val	Gln	Gly 235	Leu	Arg	Glu	Gly	Arg 240
	Ala			245				-	250			_	_	255	
	Gly		260					265					270		
	Lys	275					280					285			_
	Ala 290					295					300				
305	Pro			_	310	-		_		315					320
	Leu			325					330					335	
	Val		340					345		-			350		
	Gln	355					360					365			
	10 Jeu		10			375		_			380	_			_
385	Leu				390					395	_				400
	Asp			405					410					415	
	His		420					425					430		
	Pro	435					440					445	_		
	Gly 450					455					460				
465	Leu				470					475					480
	Pro			485					490					495	
	Gln		500					505					510		
	Glu	515					520					525			
	Thr 530					535					540				
545	Glu				550					555					560
	Glu		_	565				_	570		_			575	
	Gln		580					585					590		
	Gly	595					600				,	605			
	Leu 610					615					620				
625	Gly				630					635	_				640
	Ala			645					650					655	
	Ser		660					665			_		670		
GTD	Gln	тте	ser	Leu	rne	GIN	ATA	Met	Gln	ьys	GTA	Leu	TTE	val	Arg

99

		675					680					685			
Glu	His 690	Gly	Ile	Arg	Leu	Leu 695		Ala	Gln	Ile	Ala 700		Gly	Gly	Val
Ile 705	Asp	Pro	Val	His	Ser 710	His	Arg	Val	Pro	Val 715	Asp	Val	Ala	Tyr	Arg 720
Arg	Gly	Туг	Phe	Asp 725	Gln	Met	Leu	Asn	Leu 730	Ile	Leu	Leu	Asp	Pro 735	Ser
Asp	Asp	Thr	Lys 740	Gly	Phe	Phe	Asp	Pro 745	Asn	Thr	His	Glu	Asn 750	Leu	Thr
Tyr	Leu	Gln 755	Leu	Leu	Glu	Arg	Cys 760	Val	Arg	Asp	Pro	Glu 765	Thr	Gly	Leu
Tyr	Leu 770	Leu	Pro	Leu	Ser	Ser 775	Thr	Gln	Ser	Pro	Leu 780	Val	Asp	Ser	Ala
Thr 785	Gln	Gln	Ala	Phe	Gln 790	Asn	Leu	Leu	Leu	Ser 795	Val	Lys	Tyr	Gly	Arg 800
Phe	Gln	Gly	Gln	Arg 805	Val	Ser	Ala	Trp	Glu 810	Leu	Ile	Asn	Ser	Glu 815	Tyr
	Ser		820					825					830		
Glu	Val	Thr 835	Leu	Gly	Gln	Val	Ala 840	Lys	Leu	Leu	Glu	Ala 845	Glu	Thr	Gln
Arg	Gln 850	Ala	Asp	Ile	Met	Leu 855	Pro	Ala	Leu	Arg	Ser 860	Arg	Val	Thr	Val
865	Gln				870					875				_	880
	Leu			885					890					895	_
	Arg		900					905					910		
	Pro	915					920		_			925	_		_
	Leu 930					935					940				
945	Gly				950					955					960
	Ala			965					970			_	-	975	
	Arg		980					985					990		_
	Gln	995					1000)				1005	5		_
	Gln 1010)				1015	5				1020)			
102					1030)				1035	5				1040
	Gly			1045	ō				1050)				1055	5
	Thr		1060) '				1065	5				1070)	
Leu	Leu	Glu 1075		Cys	Pro	Arg	Asp 1080		Thr	Ser	Gly	Leu 1085		Leu	Leu
Pro	Leu 1090		Glu	Ser	Ala	Pro 1095		Leu	Pro	Thr	Glu 1100		Gln	Val	Gln
Arg 110	Ser 5	Leu	Gln	Ala	Val 1110		Gly	Ala	Lys	Asp 1115		Thr	Ser	Leu	Trp 1120
Asp	Leu	Leu	Ser	Ser 1125		His	Phe	Thr	Glu 1130		Gln	Arg	Arg	Gly 1135	Leu
Leu	Glu	Asp	Val 1140		Glu	Gly	Arg	Thr 1145		Val	Pro	Gln	Leu 1150		Ala

Ser Val Gln Arg Trp Val Gln Glu Thr Lys Leu Leu Ala Gln Ala Arg 1155 1160 Val Met Val Pro Gly Pro Arg Gly Glu Val Pro Ala Val Trp Leu Leu 1175 1180 Asp Ala Gly Ile Ile Thr Gln Glu Thr Leu Glu Ala Leu Ala Gln Gly 1185 1190 1195 1200 Thr Gln Ser Pro Ala Gln Val Ala Glu Gln Pro Ala Val Lys Ala Cys 1205 1210 1215 Leu Trp Gly Thr Gly Cys Val Ala Gly Val Leu Leu Gln Pro Ser Gly 1220 1225 1230 Ala Lys Ala Ser Ile Ala Gln Ala Val Arg Asp Gly Leu Leu Pro Thr 1235 1240 1245 Gly Leu Gly Gln Arg Leu Leu Glu Ala Gln Val Ala Ser Gly Phe Leu 1250 1255 1260 Val Asp Pro Leu Asn Asn Gln Arg Leu Ser Val Glu Asp Ala Val Lys 1265 1270 1275 1280 Val Gly Leu Val Gly Arg Glu Leu Ser Glu Gln Leu Gly Gln Ala Glu 1285 1290 1295 Arg Ala Ala Ala Gly Tyr Pro Asp Pro Tyr Ser Arg Ala Ser Leu Ser 1300 1305 1310 Leu Trp Gln Ala Met Glu Lys Gly Leu Val Pro Gln Asn Glu Gly Leu 1315 1320 1325 Pro Leu Leu Gln Val Gln Leu Ala Thr Gly Gly Val Val Asp Pro Val 1330 1335 1340 His Gly Val His Leu Pro Gln Ala Ala Cys Arg Leu Gly Leu Leu 1345 1350 1355 1360 Asp Thr Gln Thr Ser Gln Val Leu Thr Ala Val Asp Lys Asp Asn Lys 1365 1370 1375 Phe Phe Asp Pro Ser Ala Arg Asp Gln Val Thr Tyr Gln Gln Leu 1380 1385 1390 Arg Glu Arg Cys Val Cys Asp Ser Glu Thr Gly Leu Leu Leu Pro 1395 1400 1405 Leu Pro Ser Asp Thr Val Leu Glu Val Asp Asp His Thr Ala Val Ala 1410 1415 1420 Leu Arg Ala Met Lys Val Pro Val Ser Thr Gly Arg Phe Lys Gly Cys 1425 1430 1435 Ser Val Ser Leu Trp Asp Leu Leu Ser Glu Tyr Val Gly Ala Asp 1445 1450 1455 Lys Arg Arg Glu Leu Val Ala Leu Cys Arg Ser Gly Arg Ala Ala Ala 1460 1465 1470 Leu Arg Gln Val Val Ser Ala Val Thr Ala Leu Val Glu Ala Ala Glu 1475 1480 1485 Arg Gln Pro Leu Gln Ala Thr Phe Arg Gly Leu Arg Lys Gln Val Ser 1490 1495 1500 Ala Arg Asp Leu Phe Arg Ala Gln Leu Ile Ser Arg Lys Thr Leu Asp 1505 1510 1515 Glu Leu Ser Gln Gly Thr Thr Thr Val Lys Glu Val Ala Glu Met Asp 1525 1530 Ser Val Lys Arg Ser Leu Glu Gly Gly Asn Phe Ile Ala Gly Val Leu 1545 Ile Gln Gly Thr Gln Glu Arg Met Ser Ile Pro Glu Ala Leu Arg Arg 1560 His Ile Leu Arg Pro Gly Thr Ala Leu Val Leu Leu Glu Ala Gln Ala 1575 1580 Ala Thr Gly Phe Ile Ile Asp Pro Ala Glu Asn Arg Lys Leu Thr Val 1590 1595 Glu Glu Ala Phe Lys Ala Gly Met Phe Gly Lys Glu Thr Tyr Val Lys 1605 1610 Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Thr Asp Pro Tyr Thr

1620 1625 Gly Gln Gln Ile Ser Leu Phe Gln Ala Met Gln Lys Asp Leu Ile Val 1635 1640 1645 Arg Glu His Gly Ile Arg Leu Leu Glu Ala Gln Ile Ala Thr Gly Gly 1650 1655 1660 Ile Ile Asp Pro Val His Ser His Arg Val Pro Val Asp Val Ala Tyr 1665 1670 1675 1680 Arg Cys Gly Tyr Phe Asp Glu Glu Met Asn Arg Ile Leu Ala Asp Pro 1685 1690 1695 Ser Asp Asp Thr Lys Gly Phe Phe Asp Pro Asn Thr His Glu Asn Leu 1700 1705 1710 Thr Tyr Leu Gln Leu Leu Glu Arg Cys Val Glu Asp Pro Glu Thr Gly 1715 1720 1725 Leu Tyr Leu Leu Gln Ile Ile Lys Lys Gly Glu Asn Tyr Val Tyr Ile 1730 1735 1740 Asn Glu Ala Thr Arg His Val Leu Gln Ser Arg Thr Ala Lys Met Arg 1745 1750 1755 1760 Val Gly Arg Phe Ala Asp Gln Val Val Ser Phe Trp Asp Leu Leu Ser 1765 1770 1775 Ser Pro Tyr Phe Thr Glu Asp Arg Lys Arg Glu Leu Ile Gln Glu Tyr 1780 1785 1790 Gly Ala Gln Ser Gly Gly Leu Glu Lys Leu Leu Glu Ile Ile Thr Thr 1795 1800 1805 Thr Ile Glu Glu Thr Glu Thr Gln Asn Gln Gly Ile Lys Val Ala Ala 1810 \$1815 \$1820 Ile Arg Gly Glu Val Thr Ala Ala Asp Leu Phe Asn Ser Arg Val Ile 1825 1830 1835 1840 Asp Gln Lys Thr Leu His Thr Leu Arg Val Gly Arg Thr Gly Gly Gln 1845 1850 1855 Ala Leu Ser Thr Leu Glu Cys Val Lys Pro Tyr Leu Glu Gly Ser Asp 1860 1865 1870 Cys Ile Ala Gly Val Thr Val Pro Ser Thr Arg Glu Val Met Ser Leu 1875 1880 1885 His Glu Ala Ser Arg Lys Glu Leu Ile Pro Ala Ala Phe Ala Thr Trp 1890 1895 1900 Leu Leu Glu Ala Gln Ala Ala Thr Gly Phe Leu Leu Asp Pro Cys Thr 1905 1910 1915 1920 Arg Gln Lys Leu Ser Val Asp Glu Ala Val Asp Val Gly Leu Val Asn 1925 1930 1935 Glu Glu Leu Arg Glu Arg Leu Leu Lys Ala Glu Arg Ala Ala Thr Gly 1940 1945 1950 Tyr Arg Asp Pro Ala Thr Gly Asp Thr Ile Pro Leu Phe Gln Ala Met 1955 1960 1965 Gln Lys Gln Leu Ile Glu Lys Ala Glu Ala Leu Arg Leu Leu Glu Val 1970 1975 1980 Gln Val Ala Thr Gly Gly Val Ile Asp Pro Gln His His Arg Leu 1985 1990 1995 2000 Pro Leu Glu Thr Ala Tyr Arg Gly Cys Leu His Lys Asp Ile Tyr 2005 2010 2015 Ala Leu Ile Ser Asp Gln Lys His Met Arg Lys Arg Phe Val Asp Pro 2020 2025 2030 Asn Thr Gln Glu Lys Val Ser Tyr Arg Glu Leu Gln Glu Arg Cys Arg 2035 2040 2045 Pro Gln Glu Asp Thr Gly Trp Val Leu Phe Pro Val Asn Lys Ala Ala 2050 2055 2060 Arg Asp Ser Glu His Ile Asp Asp Glu Thr Arg Arg Ala Leu Glu Ala 2065 2070 2075 2080 Glu Gln Val Glu Ile Thr Val Gly Arg Phe Arg Gly Gln Lys Pro Thr 2090

Leu Trp Ala	Leu Leu 2100	Asn Ser		Tyr 2105		Thr	Glu	Glu	Lys 2110	_	Leu
Gln Leu Val . 2115	_	Tyr Arg	Thr 2120		Thr	Arg	Arg	Ala 2125		Gln	Thr
Val Ala Gln 2130	Leu Ile	Leu Glu 213		Ile	Glu	Lys	Gln 2140		Thr	Ser	Asn
Lys His Leu 2145	Trp Phe	Gln Gly 2150	Ile .	Arg	Arg	Gln 2155		Thr	Ala	Ser	Glu 2160
Leu Leu Ser	Ser Ala 2165		Thr		Glu 2170		Leu	Gln	Asp	Leu 2175	
Thr Gly Arg	Ser Thr 2180	Thr Gln		Leu 2185		Glu	Asp	Asp	Arg 2190		Lys
Arg Tyr Leu 2195		Thr Ser	Cys 2200		Ala	Gly	Val	Leu 2205		Pro	Ala
Lys Asp Gln 2210	Pro Gly	Arg Gln 221		Lys	Met	Ser	Ile 2220		Gln	Ala	Met
Trp Lys Gly 2225	Val Leu	Arg Pro 2230	Gly	Thr	Ala	Leu 2235		Leu	Leu	Glu	Ala 2240
Gln Ala Ala	2245	5		_	2250)	_			2255	5
Ser Val Glu	Glu Pro 2260	Val Pro		Gly 2265		Val	Gly	Ser	Glu 2270		Gln
Glu Lys Leu 2275			2280					2285	·		
Tyr Thr Gly 2290	Gln Gln	Ile Ser 229		Phe	Gln	Ala	Met 2300		Lys	Asp	Leu
Ile Val Arg 2305	Glu His	Gly Ile 2310	Arg	Leu		Glu 2315		Gln	Ile	Ala	Thr 2320
Gly Gly Val	Ile Asp 2325		His		His 2330	_	Val	Pro	Val	Asp 2335	
Ala Tyr Arg	Arg Gly 2340	Tyr Phe		Glu 2345		Met	Asn	Arg	Val 2350		Ala
Asp Pro Ser 2355			2360					2365	ò		
Asn Leu Thr 2370		237	5				2380)			
Thr Gly Leu 2385	Tyr Met	Leu Gln 2390	Leu .	Ala	Gly	Arg 2395		Ser	Ala	Val	His 2400
Gln Leu Ser	2405	5			2410	1				2415	5
Pro Gly Ser	Gly Ala 2420	Leu Gln		Gln 2425		Val	Ser	Val	Trp 2430		Leu
Leu Phe Tyr . 2435	-		2440	_		_		2445	ò		
Arg Tyr Arg . 2450	Ala Gly	Thr Leu 245!		Val	Glu	Glu	Leu 2460		Ala	Thr	Leu
Thr Ser Leu 2465		2470				2475	-				2480
Ala Gly Ser	Pro Arg 2485	_	Pro .	_	Glu 2490		Leu	Arg	Ala	Ala 2495	
Met Glu Val	Lys Val 2500	Gly Arg		Arg 2505		Arg	Ala	Val	Pro 2510		Trp
Asp Val Leu 2515		Gly Tyr	Val 2520		Arg	Ala	Ala	Arg 2525		Glu	Leu
Leu Ala Glu 2530		253	õ		_		2540)			_
Arg Leu Thr . 2545		2550				2555					2560
Pro Gln Leu	Gln Asp	Ala Arg	Arg	Gly	Pro	Arg	Glu	Pro	Gly	Pro	Ala

	2565	257		2575
Gly Arg Gly Asp 258		Gly Arg Ser 2585	Gln Arg Glu	Gly Gln Gly 2590
Glu Gly Glu Thr 2595	Gln Glu Ala	Ala Ala Ala 2600	a Ala Ala Ala 260	
Gln Glu Gln Thr 2610	Leu Arg Asp 2615		: Glu Val Gln 2620	Arg Gly Gln
Phe Gln Gly Arg 2625	Pro Val Ser 2630	Val Trp Asp	Val Leu Phe 2635	Ser Ser Tyr 2640
Leu Ser Glu Ala	Arg Arg Asp 2645	Glu Leu Leu 265		Ala Ala Gly 2655
Ala Leu Gly Leu 266	C	2665	_	2670
Glu Thr Glu Glu 2675		2680	268	5
Gln Val Ser Ala 2690	Ser Glu Leu 2695		Gly Ile Leu 2700	Gly Pro Glu
Thr Leu Arg Asp 2705	2710		2715	2720
Glu Met Asp Ser	2725	273	30	2735
Gly Val Leu Val 2740)	2745	_	2750
Ser Ile Tyr Gln 2755		2760	276	5
Leu Val Leu Leu 2770	Glu Ala Gln 2775		Gly Phe Val 2780	Ile Asp Pro
Val Arg Asn Leu 2785	2790	•	2795	2800
Val Gly Gly Glu	2805	281	.0	2815
Thr Gly Tyr Thr 2820)	2825		2830
Ala Met Gln Lys 2835		2840	2845	5
Glu Ala Gln Ile 2850	2855	5	2860	
Arg Val Pro Val 2865	2870		2875	2880
Met Asn Arg Val	2885	289	0	2895
Asp Pro Asn Thr 2900)	2905		2910
Cys Val Pro Asp 2915	-	2920	2925	5
Arg Gly Ser Ala 2930	2935	5	2940	
Arg Asp Ala Arg 2945	2950		2955	2960
Val Ser Val Trp	2965	297	0	2975
Arg Gln Asp Leu 2980)	2985		2990
Glu Leu Gly Ala 2995		3000	3005	;)
Ala Arg Ala Glu 3010	3015	5	3020	
Ala Leu Arg Ala 3025	Ala Thr Met 3030	Giu Val Lys	Val Gly Arg 3035	Leu Arg Gly 3040

Arg Ala Val Pr	o Val Trp Asp 3045	Val Leu Ala 305		Val Ser Gly 3055
Ala Ala Arg Gl		Ala Glu Phe 3065	Gly Ser Gly	Thr Leu Asp 3070
Leu Pro Ala Le 3075	u Thr Arg Arg	Leu Thr Ala 3080	Ile Ile Glu 308	
Glu Ala Pro Gl 3090	y Ala Arg Pro 309		Asp Ala Trp 3100	Arg Gly Pro
Arg Glu Pro Gl 3105	y Pro Ala Gly 3110	Arg Gly Asp	Gly Asp Ser 3115	Gly Arg Ser 3120
Gln Arg Glu Gl	y Gln Gly Glu 3125	Gly Glu Thr 313		Ala Ala Ala 3135
Ala Ala Ala Al 31	-	Glu Gln Thr 3145	Leu Arg Asp	Ala Thr Met 3150
Glu Val Gln Ar 3155	g Gly Gln Phe	Gln Gly Arg 3160	Pro Val Ser 316	
Val Leu Phe Se 3170	r Ser Tyr Leu 317		Arg Arg Asp 3180	Glu Leu Leu
Ala Gln His Al 3185	a Ala Gly Ala 3190	Leu Gly Leu	Pro Asp Leu 3195	Val Ala Val 3200
Leu Thr Arg Va	l Ile Glu Glu 3205	Thr Glu Glu 321		Lys Val Ser 3215
Phe Arg Gly Le 32		Val Ser Ala 3225	Ser Glu Leu	His Thr Ser 3230
Gly Ile Leu Gl 3235	y Pro Glu Thr	Leu Arg Asp 3240	Leu Ala Gln 324	
Thr Leu Gln Gl 3250	u Val Thr Glu 325		Val Lys Arg 3260	Tyr Leu Glu
Gly Thr Ser Cy 3265	s Ile Ala Gly 3270	Val Leu Val	Pro Ala Lys 3275	Asp Gln Pro 3280
Gly Arg Gln Gl	u Lys Met Ser 3285	Ile Tyr Gln 329		Lys Gly Val 3295
Leu Arg Pro Gl		Val Leu Leu 3305	Glu Ala Gln	Ala Ala Thr 3310
Gly Phe Val Il 3315	e Asp Pro Val	Arg Asn Leu 3320	Arg Leu Ser 332	
Ala Val Ala Al 3330	a Gly Val Val 333		Ile Gln Glu 3340	Lys Leu Leu
Ser Ala Glu Ar 3345	g Ala Val Thr 3350	Gly Tyr Thr	Asp Pro Tyr 3355	Thr Gly Gln 3360
Gln Ile Ser Le	3365	337	0	3375
His Gly Ile Ar 33	30	3385		3390
Asp Pro Val Hi 3395	s Ser His Arg	Val Pro Val 3400	Asp Val Ala 340	
Gly Tyr Phe As 3410	p Glu Glu Met 341		Leu Ala Asp 3420	Pro Ser Asp
Asp Thr Lys Gl 3425	y Phe Phe Asp 3430	Pro Asn Thr	His Glu Asn 3435	Leu Thr Tyr 3440
Val Gln Leu Le	a Arg Arg Cys 3445	Val Pro Asp 345	_	Gly Leu Tyr 3455
Met Leu Gln Le 34		Gly Ser Ala 3465	Vaļ His Gln	Leu Ser Glu 3470
Glu Leu Arg Cy 3475	s Ala Leu Arg	Asp Ala Arg 3480	Val Thr Pro	
Ala Leu Gln Gl 3490	y Gln Ser Val 349	Ser Val Trp		
Glu Val Ser Gl				Tyr Arg Ala

3510 3515 Gly Thr Leu Thr Val Glu Glu Leu Gly Ala Thr Leu Thr Ser Leu Leu 3525 3530 3535 Ala Gln Ala Gln Ala Gln Ala Arg Ala Glu Ala Glu Ala Gly Ser Pro 3540 3545 3550 Arg Pro Asp Pro Arg Glu Ala Leu Arg Ala Ala Thr Met Glu Val Lys 3555 3560 3565 Val Gly Arg Leu Arg Gly Arg Ala Val Pro Val Trp Asp Val Leu Ala 3570 3575 3580 Ser Gly Tyr Val Ser Gly Ala Ala Arg Glu Glu Leu Leu Ala Glu Phe **3585 3590 3595 3600** Gly Ser Gly Thr Leu Asp Leu Pro Ala Leu Thr Arg Arg Leu Thr Ala 3605 3610 3615 Ile Ile Glu Glu Ala Glu Glu Ala Pro Gly Ala Arg Pro Gln Leu Gln 3620 3625 3630 Asp Ala Trp Arg Gly Pro Arg Glu Pro Gly Pro Ala Gly Arg Gly Asp 3635 3640 3645 Gly Asp Ser Gly Arg Ser Gln Arg Glu Gly Gln Gly Glu Gly Glu Thr 3650 3655 3660 Gln Glu Ala Ala Ala Ala Ala Ala Ala Arg Arg Gln Glu Gln Thr **3665 3670 3675 3680** Leu Arg Asp Ala Thr Met Glu Val Gln Arg Gly Gln Phe Gln Gly Arg 3685 3690 3695 Pro Val Ser Val Trp Asp Val Leu Phe Ser Ser Tyr Leu Ser Glu Ala 3700 3705 3710 Arg Arg Asp Glu Leu Leu Ala Gln His Ala Ala Gly Ala Leu Gly Leu 3715 3720 3725 Pro Asp Leu Val Ala Val Leu Thr Arg Val Ile Glu Glu Thr Glu Glu 3730 3735 3740 Arg Leu Ser Lys Val Ser Phe Arg Gly Leu Arg Arg Gln Val Ser Ala **3745 3750 3755 3760** Ser Glu Leu His Thr Ser Gly Ile Leu Gly Pro Glu Thr Leu Arg Asp 3765 3770 3775 Leu Ala Gln Gly Thr Lys Thr Leu Gln Glu Val Thr Glu Met Asp Ser 3780 3785 3790 Val Lys Arg Tyr Leu Glu Gly Thr Ser Cys Ile Ala Gly Val Leu Val 3795 3800 3805 Pro Ala Lys Asp Gln Pro Gly Arg Gln Glu Lys Met Ser Ile Tyr Gln 3810 3815 3820 Ala Met Trp Lys Gly Val Leu Arg Pro Gly Thr Ala Leu Val Leu Leu 3825 3830 3835 3840 Glu Ala Gln Ala Ala Thr Gly Phe Val Ile Asp Pro Val Arg Asn Leu 3845 3850 3855 Arg Leu Ser Val Glu Glu Ala Val Ala Ala Gly Val Val Gly Glu 3860 3865 3870 Ile Gln Glu Lys Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Thr 3875 3880 3885 Asp Pro Tyr Thr Gly Gln Gln Ile Ser Leu Phe Gln Ala Met Gln Lvs 3890 3895 - 3900 Asp Leu Ile Val Arg Glu His Gly Ile Arg Leu Leu Glu Ala Gln Ile 3905 3910 3915 Ala Thr Gly Gly Val Ile Asp Pro Val His Ser His Arg Val Pro Val 3925 3930 3935 Asp Val Ala Tyr Arg Gly Tyr Phe Asp Glu Glu Met Asn Arg Val 3940 3945 3950 Leu Ala Asp Pro Ser Asp Asp Thr Lys Gly Phe Phe Asp Pro Asn Thr 3955 3960 3965 His Glu Asn Leu Thr Tyr Val Gln Leu Leu Arg Arg Cys Val Pro Asp 3975 3980

PCT/US02/18638

Pro Asp Th: 3985	Gly	Leu	Tyr 3990		Leu	Gln	Leu	Ala 399		Arg	Gly	Ser	Ala 4000
Val His Gl	ı Leu	Ser 4005	Glu		Leu	Arg	Cys 4010	Ala		Arg	Asp	Ala 401	Arg
Val Thr Pro	Gly 402	Ser		Ala	Leu	Gln 402	Gly		Ser	Val	Ser 4030	Val	
Glu Leu Let	ı Phe		Arg	Glu	Val 4040	Ser		Asp	Arg	Arg 4045	Gln	-	Leu
Leu Ser Are		Arg	Ala	Ser 4055	Thr		Thr	Val	Glu 4060	Glu		Gly	Ala
Thr Leu Th: 4065	Ser	Leu	Leu 4070	Ala		Ala	Gln	Ala 4075	Gln		Arg	Ala	Glu 4080
Ala Glu Al	a Gly	Ser 4085		Arg	Pro	Asp	Pro 4090	_	Glu	Ala	Leu	Arg 4095	
Ala Thr Me	Glu 410		Lys	Val	Gly	Arg 410		Arg	Gly	Arg	Ala 4110		Pro
Val Trp As ₁		Leu	Ala	Ser	Gly 4120		Val	Ser	Arg	Ala 4125		Arg	Glu
Glu Leu Le 4130	ı Ala	Glu	Phe	Gly 4135		Gly	Thr	Leu	Asp 4140		Pro	Ala	Leu
Thr Arg Are	g Leu	Thr	Ala 4150		Ile	Glu	Glu	Ala 415		Glu	Ala	Pro	Gly 4160
Ala Arg Pr	o;Gln	Leu 4165		Asp	Ala	Trp	Arg 417(_	Pro	Arg	Glu	Pro 4175	_
Pro Ala Gl	Arg 418		Asp	Gly	Asp	Ser 418		Arg	Ser	Gln	Arg 4190		Gly
Gln Gly Gl	95				4200)				4205	5		
Arg Arg Gl:	ı Glu	Gln	Thr	Leu	Arg	Asp	Ala	Thr	Met	Glu	Val	Gln	Arg
4210				4215					4220				
Gly Gln Ph			4230	Pro	Val			4235	Asp 5	Val			4240
Gly Gln Pho 4225 Ser Tyr Le	ı Ser	Glu 4245	4230 Ala 5	Pro) Arg	Val Arg	Asp	Glu 4250	4235 Leu O	Asp Leu	Val Ala	Gln	His 4255	4240 Ala 5
Gly Gln Photogram 4225 Ser Tyr Ler Ala Gly Ala	Ser Leu 426	Glu 4245 Gly 0	4230 Ala D Leu	Pro) Arg Pro	Val Arg Asp	Asp Leu 426	Glu 4250 Val	4235 Leu O Ala	Asp Leu Val	Val Ala Leu	Gln Thr 4270	His 4255 Arg	4240 Ala 5 Val
Gly Gln Photogram 4225 Ser Tyr Let Ala Gly Al Ile Glu Gl 42	Ser Leu 426 Thr	Glu 4245 Gly O Glu	4230 Ala S Leu Glu	Pro) Arg Pro Arg	Val Arg Asp Leu 4280	Asp Leu 426! Ser	Glu 4250 Val D Lys	4235 Leu O Ala Val	Asp Leu Val Ser	Val Ala Leu Phe 4285	Gln Thr 4270 Arg	His 4255 Arg O Gly	4240 Ala Val Leu
Gly Gln Photogram 4225 Ser Tyr Ler Ala Gly Al Ile Glu Gl 422 Arg Arg Gli 4290	Leu 426 Thr 75	Glu 4245 Gly O Glu Ser	4230 Ala Deu Glu Ala	Pro Arg Pro Arg Ser 4295	Val Arg Asp Leu 4280 Glu	Asp Leu 4269 Ser Leu	Glu 425(Val D Lys His	4235 Leu O Ala Val Thr	Asp Leu Val Ser Ser 4300	Val Ala Leu Phe 4285 Gly	Gln Thr 4270 Arg D	His 4255 Arg O Gly Leu	4240 Ala Val Leu
Gly Gln Photogram 4225 Ser Tyr Ler Ala Gly Al Ile Glu Gl 422 Arg Arg Glr 4290 Pro Glu The	Leu 426 Thr 5 Val	Glu 4245 Gly O Glu Ser Arg	A230 Ala Leu Glu Ala Asp 4310	Pro Arg Pro Arg Ser 4295 Leu	Val Arg Asp Leu 4280 Glu Ala	Asp Leu 4269 Ser Leu Gln	Glu 4250 Val 5 Lys His	4235 Leu O Ala Val Thr 4315	Asp Leu Val Ser Ser 4300 Lys	Val Ala Leu Phe 4285 Gly Thr	Gln Thr 4270 Arg Tle Leu	His 4255 Arg Gly Leu Gln	4240 Ala Val Leu Gly Glu 4320
Gly Gln Photogram 4225 Ser Tyr Ler Ala Gly Al Ile Glu Gl 427 Arg Arg Gl 4290 Pro Glu Th 4305 Val Thr Gl	Ser Leu 426 Thr 5 Val Leu	Glu 4245 Gly O Glu Ser Arg Asp	A230 Ala Leu Glu Ala Asp 4310 Ser	Pro Arg Pro Arg Ser 4295 Leu Val	Arg Asp Leu 4280 Glu Ala Lys	Asp Leu 426: Ser Leu Gln Arg	Glu 4250 Val 5 Lys His Gly Tyr 4330	4235 Leu Ala Val Thr Thr 4315 Leu	Asp Leu Val Ser Ser 4300 Lys	Val Ala Leu Phe 4285 Gly Thr	Gln Thr 4270 Arg Ile Leu Thr	His 4255 Arg Gly Leu Gln Ser 4335	4240 Ala Val Leu Gly Glu 4320 Cys
Gly Gln Photogram 4225 Ser Tyr Ler Ala Gly Al Ile Glu Gl 427 Arg Arg Glo 4290 Pro Glu Tho 4305 Val Thr Glo	1 Ser 4 Leu 426 1 Thr 75 1 Val 5 Leu 1 Met 7 Val 434	Glu 4245 Gly 0 Glu Ser Arg Asp 4325 Leu	4230 Ala Leu Glu Ala Asp 4310 Ser	Pro Arg Pro Arg Ser 4295 Leu Val	Arg Asp Leu 4280 Glu Ala Lys Ala	Asp Leu 4269 Ser Leu Gln Arg Lys 4349	Glu 4250 Val 5 Lys His Gly Tyr 4330 Asp	4235 Leu Ala Val Thr 4315 Leu Gln	Asp Leu Val Ser Ser 4300 Lys Glu	Val Ala Leu Phe 4285 Gly Thr Gly Gly	Gln Thr 4270 Arg The Leu Thr Arg 4350	His 4255 Arg Gly Leu Gln Ser 4335 Gln	4240 Ala Val Leu Gly Glu 4320 Cys Glu
Gly Gln Photogram 4225 Ser Tyr Ler Ala Gly Al Ile Glu Gl 427 Arg Arg Glr 4290 Pro Glu Thr 4305 Val Thr Glr Ile Ala Glr Lys Met Ser 43	1 Ser 4 Leu 426 1 Thr 75 1 Val 5 Leu 1 Met 7 Val 434 5 Ile	Glu 4245 Gly 0 Glu Ser Arg Asp 4325 Leu 0	4230 Ala Leu Glu Ala Asp 4310 Ser Val	Pro Arg Pro Arg Ser 4295 Leu Val Pro Ala	Arg Asp Leu 4280 Glu Ala Lys Ala Met 4360	Asp Leu 4269 Ser Leu Gln Arg Lys 4349 Trp	Glu 4250 Val 5 Lys His Gly Tyr 4330 Asp	4235 Leu Ala Val Thr Thr 4315 Leu Gln Gly	Asp Leu Val Ser Ser 4300 Lys Glu Pro	Val Ala Leu Phe 4285 Gly Thr Gly Gly Leu 4365	Gln Thr 4270 Arg Ile Leu Thr Arg 4350 Arg	His 4255 Arg Gly Leu Gln Ser 4335 Gln Pro	4240 Ala Val Leu Gly Glu 4320 Cys Glu Gly
Gly Gln Photogram 4225 Ser Tyr Leg Ala Gly Al Ile Glu Gl 4290 Pro Glu Th 4305 Val Thr Gl Ile Ala Gl Lys Met Se 4370	Leu 4260 Thr 75 Noval Met 4340 File 55	Glu 4245 Gly O Glu Ser Arg Asp 4325 Leu O Tyr	A230 Ala Leu Glu Ala Asp 4310 Ser Val Gln Leu	Pro Arg Pro Arg Ser 4295 Leu Val Pro Ala Glu 4375	Arg Asp Leu 4280 Glu Ala Lys Ala Met 4360 Ala	Leu Gln Arg Lys 434! Trp Gln	Glu 4250 Val 5 Lys His Gly Tyr 4330 Asp 5 Lys	4235 Leu Ala Val Thr 4315 Leu Gln Gly Ala	Asp Leu Val Ser Ser 4300 Lys Glu Pro Val Thr 4380	Val Ala Leu Phe 4285 Gly Thr Gly Gly Leu 4365 Gly	Thr 4270 Arg Ile Leu Thr Arg 4350 Arg	His 4255 Arg Gly Leu Gln Ser 4335 Gln Pro	4240 Ala Val Leu Gly Glu 4320 Cys Glu Gly Ile
Gly Gln Photogram 4225 Ser Tyr Leg Ala Gly Al Ile Glu Gl 4290 Pro Glu Th 4305 Val Thr Gl Ile Ala Gl Lys Met Se 4370 Asp Pro Val 4385	Leu 4260 Thr 75 Noval Met 4340 The 1655 Noval Large	Glu 4245 Gly 0 Glu Ser Arg Asp 4325 Leu 0 Tyr Leu Asn	4230 Ala Leu Glu Ala Asp 4310 Ser Val Gln Leu 4390	Pro Arg Pro Arg Ser 4295 Leu Val Pro Ala Glu 4375 Arg	Arg Asp Leu 4280 Glu Ala Lys Ala Met 4360 Ala Leu	Leu Gln Arg Lys 434! Trp Gln Ser	Glu 4250 Val 5 Lys His Gly Tyr 4330 Asp 5 Lys	4235 Leu Ala Val Thr Thr 4315 Leu Gln Gly Ala Glu 4395	Asp Leu Val Ser Ser 4300 Lys Glu Pro Val Thr 4380 Glu	Ala Leu Phe 4285 Gly Thr Gly Leu 4365 Gly Ala	Thr 4270 Arg Ile Leu Thr Arg 4350 Arg Phe	His 4255 Arg Gly Leu Gln Ser 4335 Gln Pro Val	4240 Ala Val Leu Gly Glu 4320 Cys Glu Gly Ile Ala 4400
Gly Gln Photogram 4225 Ser Tyr Leg Ala Gly Al Ile Glu Gl 4290 Pro Glu Th 4305 Val Thr Gl Ile Ala Gl Lys Met Se 4370 Asp Pro Val 4385 Gly Val Val	Leu 4260 A Leu 4260 A Thr 75 A Val 4340 A S Leu 4340 A S Leu 4 A S	Glu 4245 Gly 0 Glu Ser Arg Asp 4325 Leu 0 Tyr Leu Asn Gly 4405	A230 Ala Leu Glu Ala Asp 4310 Ser Val Gln Leu 4390 Glu 6	Pro Arg Pro Arg Ser 4295 Leu Val Pro Ala Glu 4375 Arg Ile	Arg Asp Leu 4280 Glu Ala Lys Ala Met 4360 Ala Leu Gln	Asp Leu 426: Ser Leu Gln Arg Lys 434: Trp Gln Ser Glu	Glu 4250 Val 5 Lys His Gly Tyr 4330 Asp 5 Lys Ala Val Lys 4410	4235 Leu Ala Val Thr Thr 4315 Leu Gln Gly Ala Glu 4395 Leu Clu	Asp Leu Val Ser Ser 4300 Lys Glu Pro Val Thr 4380 Glu Leu	Ala Leu Phe 4285 Gly Thr Gly Leu 4365 Gly Ala Ser	Thr 4270 Arg Ile Leu Thr Arg 4350 Arg Phe Val	His 4255 Arg Gly Leu Gln Ser 4335 Gln Pro Val Ala Glu 4415	4240 Ala Val Leu Gly Glu 4320 Cys Glu Gly Ile Ala 4400 Arg
Gly Gln Photogram 4225 Ser Tyr Lei Ala Gly Al Ile Glu Gl: 4290 Pro Glu Th: 4305 Val Thr Gl: Ile Ala Gl: Lys Met Se: 4370 Asp Pro Va: 4385 Gly Val Va: Ala Val Th:	Leu 4260 Thr 75 Noval Met 4340 The 55 Noval Arg	Glu 4245 Gly 0 Glu Ser Arg Asp 4325 Leu 0 Tyr Leu Asn Gly 4405 Tyr 0	A230 Ala Leu Ala Asp 4310 Ser Val Gln Leu 4390 Glu Thr	Pro Arg Pro Arg Ser 4295 Leu Val Pro Ala Glu 4375 Arg Ile Asp	Arg Asp Leu 4280 Glu Ala Lys Ala Met 4360 Ala Leu Gln Pro	Leu 426: Ser Leu Gln Arg Lys 434: Trp Gln Ser Glu Tyr 442:	Glu 4250 Val 5 Lys His Gly Tyr 4330 Asp 5 Lys Ala Val Lys 4410 Thr	4235 Leu Ala Val Thr Thr 4315 Leu Gln Gly Ala Glu 4395 Leu Gly	Asp Leu Val Ser 4300 Lys Glu Pro Val Thr 4380 Glu Leu Gln	Ala Leu Phe 4285 Gly Thr Gly Leu 4365 Gly Ala Ser Gln	Thr 4270 Arg Ile Leu Thr Arg 4350 Arg Phe Val Ala Ile 4430	His 4255 Arg Gly Leu Gln Ser 4335 Gln Pro Val Ala Glu 4415 Ser	4240 Ala Val Leu Gly Glu 4320 Cys Glu Gly Ile Ala 4400 Arg
Gly Gln Photogram 4225 Ser Tyr Leg Ala Gly Al Ile Glu Gl 4290 Pro Glu Th 4305 Val Thr Gl Ile Ala Gl Lys Met Se 4370 Asp Pro Val 4385 Gly Val Val	Leu 4260 Thr 75 Noval Met 4340 The 12 Leu Met 12 Leu Met 13 Leu Met 14 Leu Met 15 Leu Me	Glu 4245 Gly 0 Glu Ser Arg Asp 4325 Leu 0 Tyr Leu Asn Gly 4405 Tyr 0 Gln	4230 Ala Leu Glu Ala Asp 4310 Ser Val Gln Leu 4390 Glu Thr	Pro Arg Pro Arg Ser 4295 Leu Val Pro Ala Glu 4375 Arg Ile Asp	Arg Asp Leu 4280 Glu Ala Lys Ala Met 4360 Ala Cheu Gln Pro Leu 4440	Asp Leu 426 Ser Leu Gln Arg Lys 434 Trp Gln Ser Glu Tyr 442 Ile	Glu 4250 Val 5 Lys His Gly Tyr 4330 Asp 5 Lys Ala Val Lys 4410 Thr 5 Val	4235 Leu Ala Val Thr Thr 4315 Leu Gln Gly Ala Glu 4395 Leu Gly Arg	Asp Leu Val Ser 4300 Lys Glu Pro Val Thr 4380 Glu Colu Colu Glu Glu Glu	Val Ala Leu Phe 4285 Gly Thr Gly Leu 4365 Gly Ala Ser Gln His 4445	Thr 4270 Arg Ile Leu Thr Arg 4350 Phe Val Ala Ile 4430 Gly	His 4255 Arg Gly Leu Gln Ser 4335 Gln Pro Val Ala Glu 4415 Ser)	4240 Ala Val Leu Gly Glu 4320 Cys Glu Gly Ile Ala 4400 Arg Leu Arg

4455 4460 Ser His Arg Val Pro Val Asp Val Ala Tyr Arg Arg Gly Tyr Phe Asp 4465 4470 4475 4480 Glu Glu Met Asn Arg Val Leu Ala Asp Pro Ser Asp Asp Thr Lys Gly 4485 4490 4495 Phe Phe Asp Pro Asn Thr His Glu Asn Leu Thr Tyr Val Gln Leu Leu 4500 4505 4510 Arg Arg Cys Val Pro Asp Pro Asp Thr Gly Leu Tyr Met Leu Gln Leu 4515 4520 4525 Ala Gly Arg Gly Ser Ala Val His Gln Leu Ser Glu Glu Leu Arg Cys 4530 4535 4540 Ala Leu Arg Asp Ala Arg Val Thr Pro Gly Ser Gly Ala Leu Gln Gly 4545 4550 4555 4560 Gln Ser Val Ser Val Trp Glu Leu Leu Phe Tyr Arg Glu Val Ser Glu 4565 4570 4575 Asp Arg Arg Gln Asp Leu Leu Ser Arg Tyr Arg Ala Gly Thr Leu Thr 4580 4585 4590 Val Glu Glu Leu Gly Ala Thr Leu Thr Ser Leu Leu Ala Gln Ala Gln 4595 4600 4605 Ala Gln Ala Arg Ala Glu Ala Glu Ala Gly Ser Pro Arg Pro Asp Pro 4610 4615 4620 Arg Glu Ala Leu Arg Ala Ala Thr Met Glu Val Lys Val Gly Arg Leu 4625 4630 4635 Arg Gly Arg Ala Val Pro Val Trp Asp Val Leu Ala Ser Gly Tyr Val 4645 4650 4655 Ser Gly Ala Ala Arg Glu Glu Leu Leu Ala Glu Phe Gly Ser Gly Thr 4660 4665 4670 Leu Asp Leu Pro Ala Leu Thr Arg Arg Leu Thr Ala Ile Ile Glu Glu 4675 4680 4685 Ala Glu Glu Ala Pro Gly Ala Arg Pro Gln Leu Gln Asp Ala Trp Arg 4690 4695 4700 Gly Pro Arg Glu Pro Gly Pro Ala Gly Arg Gly Asp Gly Asp Ser Gly 4705 4710 4715 4720Arg Ser Gln Arg Glu Gly Gln Gly Glu Gly Glu Thr Gln Glu Ala Ala 4725 4730 4735 Ala Ala Ala Ala Ala Arg Arg Gln Glu Gln Thr Leu Arg Asp Ala 4740 4745 4750 Thr Met Glu Val Gln Arg Gly Gln Phe Gln Gly Arg Pro Val Ser Val 4755 4760 4765 Trp Asp Val Leu Phe Ser Ser Tyr Leu Ser Glu Ala Arg Arg Asp Glu 4770 4775 4780 Leu Leu Ala Gln His Ala Ala Gly Ala Leu Gly Leu Pro Asp Leu Val 4785 4790 4795 4800 Ala Val Leu Thr Arg Val Ile Glu Glu Thr Glu Glu Arg Leu Ser Lys 4805 4810 4815 Val Ser Phe Arg Gly Leu Arg Arg Gln Val Ser Ala Ser Glu Leu His 4820 4825 4830 Thr Ser Gly Ile Leu Gly Pro Glu Thr Leu Arg Asp Leu Ala Gln Gly 4835 4840 4845 Thr Lys Thr Leu Gln Glu Val Thr Glu Met Asp Ser Val Lys Arg Tyr 4850 4855 4860 Leu Glu Gly Thr Ser Cys Ile Ala Gly Val Leu Val Pro Ala Lys Asp 4865 4870 4875 4880 Gln Pro Gly Arg Gln Glu Lys Met Ser Ile Tyr Gln Ala Met Trp Lys 4885 4890 4895 Gly Val Leu Arg Pro Gly Thr Ala Leu Val Leu Leu Glu Ala Gln Ala 4900 4905 4910 Ala Thr Gly Phe Val Ile Asp Pro Val Arg Asn Leu Arg Leu Ser Val 4920

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Arg Glu His Gly Ile Arg Leu Leu Glu Ala Gln Ile Ala Thr Gly Gly 4980 4985 4990

Val Ile Asp Pro Val His Ser His Arg Val Pro Val Asp Val Ala Tyr 4995 5000 5005

Arg Arg Gly Tyr Phe Asp Glu Glu Met Asn Arg Val Leu Ala Asp Pro 5010 5015 5020

Ser Asp Asp Thr Lys Gly Phe Phe Asp Pro Asn Thr His Glu Asn Leu 5025 5030 5035 5040

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<211> 1664

<212> DNA

<213> Homo sapiens

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<210> 54

<211> 313

<212> PRT

<213> Homo sapiens

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<211> 3334
<212> DNA
<213> Homo sapiens
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<211> 509

<212> PRT

<213> Homo sapiens

<400> 56

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Arg	Leu	Val	Lys	Phe 85	Leu	Pro	Glu	Ile	Leu 90	Ala	Leu	Gln	Arg	Asp 95	Leu
Val	Lys	Gln	Phe 100	Gln	Asn	Val	Gln	Gln 105	Val	Glu	Tyr	Ser	Ser 110	Ile	Arg
Gly	Phe	Leu 115	Ser	Lys	His	Ser	Ser 120	Asp	Gly	Leu	Arg	Gln 125	Leu	Leu	His
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Leu 145	Glu	Thr	Asn	Gly	Glu 150	Ile	Asn	Leu	Pro	Lys 155	Asp	Tyr	Cys	Ser	Thr 160
			Leu	165					170				_	175	_
			Leu 180					185					190	_	
		195	Ile				200					205			
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			Glu	245					250					255	
			Arg 260					265					270		
		275	Lys				280					285			
	290		Leu			295					300			_	
305			Ser		310					315					320
			Cys	325					330					335	
			Ala 340					345					350		
		355	Leu				360					365			
	370		Cys			375					380				
385			Lys		390					395					400
			Ser	405					410					415	
ГÀЗ	Leu	Leu	Ser 420	Thr	Phe	Leu	Asn	Gln 425	Thr	Gly	Leu	Asp	Ala 430	Phe	Leu
Leu	Glu	Leu 435	His	Glu	Met	Ile	Ile 440	Leu	Lys	Leu	Lys	Asn 445	Pro	Gln	Thr
	450		Glu			455					460				
Val 465	Ser	Tyr	Met	Gln	Thr 470	Lys	Glu	Ser	Glu	Ile 475	Leu	Pro	Glu	Met	Ala 480
			Pro	485					490				Ser	Val 495	Trp
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<211> 1760
<212> DNA
<213> Homo sapiens
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Leu Glu Ser Ser Asp Cys Glu Ser Leu Asp Ser Ser Asn Ser Gly Phe
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Gly Pro Glu Glu Asp Thr Ala Tyr Leu Asp Gly Val Ser Leu Pro Asp
                    70
                                        75
Phe Glu Leu Leu Ser Asp Pro Glu Asp Glu His Leu Cys Ala Asn Leu
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Met Gln Leu Leu Gln Glu Ser Leu Ala Gln Ala Arg Leu Gly Ser Arg
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117

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Arg Pro Tyr Pro Pro Asn Val Gly Glu Glu Ile Gln Ile Gly His Ile
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Pro Arg Glu Asp Val Asp Tyr His Leu Tyr Pro His Gly Pro Gly Leu
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Asn Pro Asn Ala Ser Thr Gly Gln Glu Ala Leu Ser Gln Thr Thr Ile
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Ser Trp Ala Pro Phe Gln Asp Thr Ser Glu Tyr Ile Ile Ser Cys His
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Pro Val Gly Thr Asp Glu Glu Pro Leu Gln Phe Arg Val Pro Gly Thr
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Glu Val Val Thr Val Gly Asn Ser Val Asn Glu Gly Leu Asn Gln Pro
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Thr Asp Asp Ser Cys Phe Asp Pro Tyr Thr Val Ser His Tyr Ala Val
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Gln Cys Leu Gly Phe Gly Ser Gly His Phe Arg Cys Asp Ser Ser Arg
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Trp Cys His Asp Asn Gly Val Asn Tyr Lys Ile Gly Glu Lys Trp Asp
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Gly Lys Gly Glu Phe Lys Cys Asp Pro His Glu Ala Thr Cys Tyr Asp
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Asp Gly Lys Thr Tyr His Val Gly Glu Gln Trp Gln Lys Glu Tyr Leu
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Gly Ala Ile Cys Ser Cys Thr Cys Phe Gly Gly Gln Arg Gly Trp Arg
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Cys Asp Asn Cys Arg Arg Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr
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                              745
Thr Gly Gln Ser Tyr Asn Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr
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<211> 7680

<212> DNA

<213> Homo sapiens

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Thr Gln Thr Tyr Gly Gly Asn Leu Asn Gly Glu Pro Cys Val Leu Pro

Phe Thr Tyr Asn Gly Arg Thr Phe Tyr Ser Cys Thr Thr Glu Gly Arg 340 345 350 Gln Asp Gly His Leu Trp Cys Ser Thr Thr Ser Asn Tyr Glu Gln Asp

360

315

365

330

310

325

355

Gln	Lys 370	Tyr	Ser	Phe	Cys	Thr 375	Asp	His	Thr	Val	Leu 380	Val	Gln	Thr	Gln
Gly 385	Gly	Asn	Ser	Asn	Gly 390	Ala	Leu	Cys	His	Phe 395		Phe	Leu	Tyr	Asn 400
Asn	His	Asn	Tyr	Thr 405	Asp	Суѕ	Thr	Ser	Glu 410	Gly	Arg	Arg	Asp	Asn 415	Met
Lys	Trp	Cys	Gly 420	Thr	Thr	Gln	Asn	Tyr 425	Asp	Ala	Asp	Gln	Lys 430	Phe	Gly
Phe	Cys	Pro 435	Met	Ala	Ala	His	Glu 440	Glu	Ile	Cys	Thr	Thr 445	Asn	Glu	Gly
Val	Met 450	Tyr	Arg	Ile	Gly	Asp 455	Gln	Trp	Asp	Lys	Gln 460	His	Asp	Met	Gly
His 465	Met	Met	Arg	Cys	Thr 470	Cys	Val	Gly	Asn	Gly 475	Arg	Gly	Glu	Trp	Thr 480
Cys	Ile	Ala	Tyr	Ser 485	Gln	Leu	Arg	Asp	Gln 490	Cys	Ile	Val	Asp	Asp 495	Ile
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		515					520			Arg		525			
Asp	Pro 530	Val	Asp	Gln	Cys	Gln 535	Asp	Ser	Glu	Thr	Gly 540	Thr	Phe	Tyr	Gln
545					550		-			Gly 555		-			560
				565					570	His				575	
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	690					695				Glu	700				
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				725					730	Glu				735	
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785					790					Val 795					800
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			820					825		Thr			830		
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Val 865	Val	Ile	Gln	Gln	Glu 870	Thr	Thr	Gly	Thr	Pro 875	Arg	Ser	Asp	Thr	Val 880
Pro	Ser	Pro	Arg	Asp 885	Leu	Gln	Phe	Val	Glu 890	Val	Thr	Asp	Val	Lys 895	Val
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Ile	Ser 930	Arg	Asn	Thr	Phe	Ala 935	Glu	Val	Thr	Gly	Leu 940	Ser	Pro	Gly	Val
Thr 945	Tyr	Туг	Phe	Lys	Val 950	Phe	Ala	Val	Ser	His 955	Gly	Arg	Glu	Ser	Lys 960
Pro	Leu	Thr	Ala	Gln 965	Gln	Thr	Thr	Lys	Leu 970	Asp	Ala	Pro	Thr	Asn 975	Leu
Gln	Phe	Val	Asn 980	Glu	Thr	Asp	Ser	Thr 985	Val	Leu	Val	Arg	Trp 990	Thr	Pro
Pro	Arg	Ala 995	Gln	Ile	Thr	Gly	Tyr 1000	-	Leu	Thr	Val	Gly 1005		Thr	Arg
	1010)		_		Tyr 1015	5				1020)		_	_
1025	5				1030					1035	5				1040
				1045	5	Glu			1050)				1055	5
			1060) _		Ser		1065	5	_			1070)	
		107	5			Thr	1080)				1085	5	-	
	1090)				Ser 1095	5				1100)			
1105	5				1110					1115	5			-	1120
				1125	5	Gln			1130)				1135	5
			1140)		Val		1145	ŝ				1150)	
		115	5			Pro	1160)				1165	Š		
	1170)				Asp 1175	5				1180)			
1185	5		_		1190					1195	5				1200
				1205	5	Phe			1210)				1215	5
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1265	5	_			1270				_	1275	ō			_	1280
				1285	5	Leu			1290)		_		1295	j
Val	Leu	Thr	Asn 1300		Leu	Pro	Gly	Thr 1305		Tyr	Val	Val	Ser 1310		Ser

Ser Val Tyr Glu Gln His Glu Ser Thr Pro Leu Arg Gly Arg Gln Lys 1315 1320 1325 Thr Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala 1330 1335 1340
Asn Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly 1345 1350 1355 1360 Tyr Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu $1365 \hspace{1.5cm} 1370 \hspace{1.5cm} 1375$ Asp Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr 1380 1385 1390 Pro Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu 1395 1400 1405 Glu Ser Pro Leu Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro 1410 1415 1420 Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser 1425 1430 1435 1440 Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly 1445 1450 1455 Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser 1460 1465 1470 Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr 1475 1480 1485 Ile Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser 1490 1495 1500 Lys Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln 1505 1510 1515 1520 Met Gln Val Thr Asp Val Gln Asp Asn Ser Ile Ser Val Lys Trp Leu 1525 1530 1535 Pro Ser Ser Pro Val Thr Gly Tyr Arg Val Thr Thr Pro Lys 1540 1545 1550 Asn Gly Pro Gly Pro Thr Lys Thr Lys Thr Ala Gly Pro Asp Gln Thr 1555 1560 1565 Glu Met Thr Ile Glu Gly Leu Gln Pro Thr Val Glu Tyr Val Val Ser 1570 1575 1580 Val Tyr Ala Gln Asn Pro Ser Gly Glu Ser Gln Pro Leu Val Gln Thr 1585 1590 1595 Ala Val Thr Asn Ile Asp Arg Pro Lys Gly Leu Ala Phe Thr Asp Val 1605 1610 1615 Asp Val Asp Ser Ile Lys Ile Ala Trp Glu Ser Pro Gln Gly Gln Val 1620 1625 1630 Ser Arg Tyr Arg Val Thr Tyr Ser Ser Pro Glu Asp Gly Ile His Glu 1635 1640 1645 Leu Phe Pro Ala Pro Asp Gly Glu Glu Asp Thr Ala Glu Leu Gln Gly 1650 1655 1660 Leu Arg Pro Gly Ser Glu Tyr Thr Val Ser Val Val Ala Leu His Asp 1670 1675 Asp Met Glu Ser Gln Pro Leu Ile Gly Thr Gln Ser Thr Ala Ile Pro 1685 1690 1695 Ala Pro Thr Asp Leu Lys Phe Thr Gln Val Thr Pro Thr Ser Leu Ser 1700 1705 Ala Gln Trp Thr Pro Pro Asn Val Gln Leu Thr Gly Tyr Arg Val Arg 1720 1725 Val Thr Pro Lys Glu Lys Thr Gly Pro Met Lys Glu Ile Asn Leu Ala 1730 1735 1740 Pro Asp Ser Ser Val Val Val Ser Gly Leu Met Val Ala Thr Lys 1755 1760 1750 Tyr Glu Val Ser Val Tyr Ala Leu Lys Asp Thr Leu Thr Ser Arg Pro 1765 1770 Ala Gln Gly Val Val Thr Thr Leu Glu Asn Val Ser Pro Pro Arg Arg

1780 1785 Ala Arg Val Thr Asp Ala Thr Glu Thr Thr Ile Thr Ile Ser Trp Arg 1795 1800 1805 Thr Lys Thr Glu Thr Ile Thr Gly Phe Gln Val Asp Ala Val Pro Ala 1810 1815 1820 Asn Gly Gln Thr Pro Ile Gln Arg Thr Ile Lys Pro Asp Val Arg Ser 1825 1830 1835 1840 Tyr Thr Ile Thr Gly Leu Gln Pro Gly Thr Asp Tyr Lys Ile Tyr Leu 1845 1850 1855 Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser Pro Val Val Ile Asp Ala 1860 1865 1870 Ser Thr Ala Ile Asp Ala Pro Ser Asn Leu Arg Phe Leu Ala Thr Thr 1875 1880 1885 Pro Asn Ser Leu Leu Val Ser Trp Gln Pro Pro Arg Ala Arg Ile Thr 1890 1895 1900 Gly Tyr Ile Ile Lys Tyr Glu Lys Pro Gly Ser Pro Pro Arg Glu Val 1905 1910 1915 1920 Val Pro Arg Pro Arg Pro Gly Val Thr Glu Ala Thr Ile Thr Gly Leu 1925 1930 1935 Glu Pro Gly Thr Glu Tyr Thr Ile Tyr Val Ile Ala Leu Lys Asn Asn 1940 1945 1950 Gln Lys Ser Glu Pro Leu Ile Gly Arg Lys Lys Thr Asp Glu Leu Pro 1955 1960 1965 Gln Leu Val Thr Leu Pro His Pro Asn Leu His Gly Pro Glu Ile Leu 1970 1975 1980 Asp Val Pro Ser Thr Val Gln Lys Thr Pro Phe Val Thr His Pro Gly 1985 1990 1995 2000 Tyr Asp Thr Gly Asn Gly Ile Gln Leu Pro Gly Thr Ser Gly Gln Gln 2005 2010 2015 Pro Ser Val Gly Gln Gln Met Ile Phe Glu Glu His Gly Phe Arg Arg 2020 2025 2030 Thr Thr Pro Pro Thr Thr Ala Thr Pro Ile Arg His Arg Pro Arg Pro 2035 2040 2045 Tyr Pro Pro Asn Val Gly Gln Glu Ala Leu Ser Gln Thr Thr Ile Ser 2050 2055 2060 Trp Ala Pro Phe Gln Asp Thr Ser Glu Tyr Ile Ile Ser Cys His Pro 2065 2070 2075 2080 Val Gly Thr Asp Glu Glu Pro Leu Gln Phe Arg Val Pro Gly Thr Ser 2085 2090 2095 Thr Ser Ala Thr Leu Thr Gly Leu Thr Arg Gly Ala Thr Tyr Asn Ile 2100 2105 2110 Ile Val Glu Ala Leu Lys Asp Gln Gln Arg His Lys Val Arg Glu Glu 2115 2120 2125 Val Val Thr Val Gly Asn Ser Val Asn Glu Gly Leu Asn Gln Pro Thr 2130 2135 2140 Asp Asp Ser Cys Phe Asp Pro Tyr Thr Val Ser His Tyr Ala Val Gly 2145 2150 2155 2160 Asp Glu Trp Glu Arg Met Ser Glu Ser Gly Phe Lys Leu Leu Cys Gln 2165 2170 2175 Cys Leu Gly Phe Gly Ser Gly His Phe Arg Cys Asp Ser Ser Arg Trp 2180 2185 Cys His Asp Asn Gly Val Asn Tyr Lys Ile Gly Glu Lys Trp Asp Arg 2195 2200 2205 Gln Gly Glu Asn Gly Gln Met Met Ser Cys Thr Cys Leu Gly Asn Gly 2210 2215 2220 Lys Gly Glu Phe Lys Cys Asp Pro His Glu Ala Thr Cys Tyr Asp Asp 2225 2230 2235 Gly Lys Thr Tyr His Val Gly Glu Gln Trp Gln Lys Glu Tyr Leu Gly 2245 2250

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Asp Asn Cys Arg Arg Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr Thr 2275 2280 2285

Gly Gln Ser Tyr Asn Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr Asn 2290 2295 2300

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<212> DNA

<213> Homo sapiens

<400> 65

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<210> 66

<211> 326

<212> PRT

<213> Homo sapiens

<400> 66

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126

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Pro Thr Ile Asn Ala Ile Thr Thr Ser Gln Asp Leu Gln Trp Met Val
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Gln Pro Thr Val Ile Thr Ser Met Ser Asn Pro Tyr Pro Arg Ser His
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                                     75
Pro Tyr Ser Pro Leu Pro Gly Leu Ala Ser Val Pro Gly His Met Ala
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Leu Pro Arg Pro Gly Val Ile Lys Thr Ile Gly Thr Thr Val Gly Arg
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Arg Arg Arg Asp Glu Gln Leu Ser Pro Glu Glu Glu Lys Arg Arg
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Ile Arg Arg Glu Arg Asn Lys Leu Ala Ala Lys Cys Arg Asn Arg
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Arg Arg Glu Leu Thr Glu Lys Leu Gln Ala Glu Thr Glu Glu Leu Glu
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Glu Glu Lys Ser Gly Leu Gln Lys Glu Ile Ala Glu Leu Gln Lys Glu
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              165
                                                    175
Lys Glu Lys Leu Glu Phe Met Leu Val Ala His Gly Pro Val Cys Lys
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           180
Ile Ser Pro Glu Glu Arg Arg Ser Pro Pro Ala Pro Gly Leu Gln Pro
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Met Arg Ser Gly Gly Ser Val Gly Ala Val Val Lys Gln Glu
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Pro Leu Glu Glu Asp Ser Pro Ser Ser Ser Ala Gly Leu Asp Lys
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Ala Gln Arg Ser Val Ile Lys Pro Ile Ser Ile Ala Gly Gly Phe Tyr
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Gly Glu Glu Pro Leu His Thr Pro Ile Val Val Thr Ser Thr Pro Ala
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                             265
Val Thr Pro Gly Thr Ser Asn Leu Val Phe Thr Tyr Pro Ser Val Leu
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                         280
                                            285
Glu Gln Glu Ser Pro Ala Ser Pro Ser Glu Ser Cys Ser Lys Ala His
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Arg Arg Ser Ser Ser Gly Asp Gln Ser Ser Asp Ser Leu Asn Ser
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Pro Thr Leu Leu Ala Leu
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<210> 67
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<220>

<221> misc feature

<222> 2087, 2093, 2098

<223> n = A, T, C or G

<400> 67

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<211> 3602

<212> DNA

<213> Homo sapiens

PCT/US02/18638

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<210> 68

<211> 3252

<212> DNA

<213> Homo sapiens

WO 02/101075 PCT/US02/18638 128

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<220>
<221> misc feature
<222> 779
<223> n = A, T, C or G
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<400> 68

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<210> 69
<211> 756
<212> PRT
<213> Homo sapiens
<400> 69
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1 5
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Phe Leu Asp Thr Ile Ile Arg Ala Glu Cys Phe Leu Gln Glu Gly Tyr
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Tyr Ser Cys Glu Ala Phe Leu Tyr Lys Ser Leu Pro Leu Trp Asp Gly
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Leu Ser Cys Arg Ser Gln Phe Leu Gln Leu Val Ser Trp Ile Pro Phe
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Ser Ser Phe Ser Glu Val Lys Pro Leu Leu Phe Asp His Leu Ala Gln
                  470
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Leu Phe Phe Thr Ser Thr Ile Tyr Phe Lys Cys Ser Val Leu Gln Ser
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Leu Lys Glu Leu Leu Gln Asn Trp Leu Leu Trp Leu Ser Met Asp Ile
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His Met Lys Pro Val Thr Asn Ser Pro Leu Glu Thr Thr Leu Gly Gly
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Ser Met Asn Cys Val Ser Lys Leu Ile His Tyr Val Gly Trp Leu Ser
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Thr Thr Ala Met Arg Leu Glu Ser Asn Asn Thr Phe Leu Leu His Phe
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Leu Pro Leu Val Val Leu Phe Pro Pro Gly Ile Phe Tyr Ser Ala Leu
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Leu Ser Leu Asp Thr Ser Ile Leu Asn Gln Leu Cys Phe Ile Met His
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Arg Tyr Arg Lys Asn Leu Thr Ala Ala Lys Lys Asn Glu Leu Val Gln
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Lys Thr Lys Ser Glu Phe Asn Phe Ser Ser Lys Thr Tyr Gln Glu Phe
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Asn Tyr Tyr Leu Thr Ser Met Val Gly Cys Leu Trp Thr Ser Lys Pro
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Phe Ala Lys Gly Ile Tyr Ile Asp Pro Glu Ile Leu Glu Lys Thr Gly
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Val Ala Glu Tyr Lys Asn Ser Leu Asn Val Val His His Pro Ser Phe
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                                             685
Leu Ser Tyr Ala Val Ser Phe Leu Leu Gln Glu Ser Pro Glu Glu Arg
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                                         700
Thr Val Asn Val Ser Ser Ile Arg Gly Lys Lys Trp Ser Trp Tyr Leu
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                                      715
Asp Tyr Leu Phe Ser Gln Gly Leu Gln Gly Leu Lys Leu Phe Ile Arg
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<210> 70

<211> 1559

<212> DNA

<213> Homo sapiens

<400> 70

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<211> 338
<212> PRT
<213> Homo sapiens
<400> 71
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Gly Val Asn Asp Ser Phe Pro Asp Gly Asp Tyr Asp Ala Asn Leu Glu
                            40
Ala Ala Pro Cys His Ser Cys Asn Leu Leu Asp Asp Ser Ala Leu
                        55
Pro Phe Phe Ile Leu Thr Ser Val Leu Gly Ile Leu Ala Ser Ser Thr
                    70
                                        75
Val Leu Phe Met Leu Phe Arg Pro Leu Phe Arg Trp Gln Leu Cys Pro
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Gly Trp Pro Val Leu Ala Gln Leu Ala Val Gly Ser Ala Leu Phe Ser
                                105
Ile Val Val Pro Val Leu Ala Pro Gly Leu Gly Ser Thr Arg Ser Ser
                            120
Ala Leu Cys Ser Leu Gly Tyr Cys Val Trp Tyr Gly Ser Ala Phe Ala
                        135
Gln Ala Leu Leu Gly Cys His Ala Ser Leu Gly His Arg Leu Gly
                    150
                                        155
Ala Gly Gln Val Pro Gly Leu Thr Leu Gly Leu Thr Val Gly Ile Trp
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Gly Val Ala Ala Leu Leu Thr Leu Pro Val Thr Leu Ala Ser Gly Ala
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Ser Gly Gly Leu Cys Thr Leu Ile Tyr Ser Thr Glu Leu Lys Ala Leu
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Gln Ala Thr His Thr Val Ala Cys Leu Ala Ile Phe Val Leu Leu Pro
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Leu Gly Leu Phe Gly Ala Lys Gly Leu Lys Lys Ala Leu Gly Met Gly
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Pro His Gly Val Val Leu Gly Leu Asp Phe Leu Val Arg Ser Lys Leu
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Leu Leu Ser Thr Cys Leu Ala Gln Gln Ala Leu Asp Leu Leu Leu
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Asn Leu Ala Glu Ala Leu Ala Ile Leu His Cys Val Ala Thr Pro Leu
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Leu Leu Ala Leu Phe Cys His Gln Ala Thr Arg Thr Leu Leu Pro Ser
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Gly Gly Leu Ala Val Ala Gly Leu Pro Ala Leu Gly Phe Thr Gly Ala
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Ile Leu Asn Gly Gly Gly Val Pro Ala Gly Gly Leu Val Ala Thr Leu
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WO 02/101075 PCT/US02/18638 134

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Arg Glu Ile Val Ala Leu Lys Thr Lys Leu Lys Glu Cys Glu Ala Ser
Lys Asp Gln Asn Thr Pro Val Val His Pro Pro Pro Thr Pro Gly Ser
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Cys Gly His Gly Gly Val Val Asn Ile Ser Lys Pro Ser Val Val Gln
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Tyr Ser Pro Gln His Pro Asn Lys Gly Leu Tyr Trp Val Ala Pro Leu
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WO 02/101075 PCT/US02/18638

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PCT/US02/18638

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Thr Tyr Pro Pro Leu His Gly Pro Met Arg Phe Pro Pro Ser Leu Ser 260 265 270

Glu Thr Asn Lys Gly Leu Arg Gly Arg Gly Pro Pro Pro Ser Trp Ala 275 280 285

Ser	Glu 290	Pro	Glu	Arg	Pro	Ser 295	Ile	Leu	Ser	Ala	Ser 300	Glu	Leu	Lys	Glu
Leu 305	Asp	Lys	Phe	Asp	Asn 310	Leu	Asp	Ala	Glu	Ala 315	Asp	Glu	Gly	Trp	Ala 320
Gly	Ala	GIn	Met	Glu 325	Val	Asp	Tyr	Thr	Glu 330	Gln	Leu	Asn	Phe	Ser 335	Asp
Asp	Asp	Glu	Gln 340	Gly	Ser	Asn	Ser	Pro 345	Lys	Glu	Asn	Asn	Ser 350	Glu	Asp
Gln	Gly	<i>Ser</i> 355	Lys	Ala	Ser	Glu	<i>As</i> n 360	Asn	Glu	Asn	Lys	<i>Lys</i> 365	Glu	Thr	Asp
Glu	Val 370	Ser	Asn	Thr	Lys	Ser 375	Ser	Ser	Gln	Ile	Pro 380	Ala	Gln	Pro	Ser
385	Ala				390	_		_		395					400
	Thr			405					410					415	
	Pro		420					425					430		
	Ser	435					440					445			
	Arg 450					455					460	_		-	_
465	Arg				470	_				475		_	_		480
	Ala		-	485		_		_	490	_		_		495	
	Gln		500					505				_	510	_	
	Glu	515					520					525		_	
	Glu 530					535					540	_		-	
545	Glu				550					555				_	560
	Glu			565					570					575	
	Gln		580					585					590		
	Glu	595					600					605			
	Met 610					615					620				
625	Pro				630					635					640
	Pro			645					650					655	
	Ala		660					665					670		
	Arg	675					680			_		685		_	
	Gln 690					695					700				
Ser 705					710					715					720
	Gln			725					730					735	
	Leu		740					745		_			750		-
Pro	Ala	Met	Asp	Ile	Pro	Pro	Ile	His	Pro	Gly	Met	Ile	Pro	Pro	Lys

PCT/US02/18638

		755					760					765			
Pro	Leu 770		Arg	Arg	Asp	Gln 775		Glu	Gly	Ser	Pro 780		Ser	Ser	Glu
Ser 785	Phe	Glu	His	Ile	Ala 790	Arg	Ser	Ala	Arg	Asp 795	His	Ala	Ile	Ser	Leu 800
Ser	Glu	Pro	Arg	Met 805	Leu	Trp	Gly	Ser	Asp 810	Pro	Tyr	Pro	His	Ala 815	Glu
			820					825		Glu			830	_	
		835					840			Ile		845			
	850					855				Lys	860				
865					870					Leu 875		_			880
				885					890	Asn				895	
			900		-			905		Pro			910	_	
		915					920			Arg		925			
	930					935				Arg	940				
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				965					970	Gly				975	
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		995					1000)		Glu		1005	5	_	_
	1010)				1015	5			Pro	1020)			
1025	5				1030)				Glu 1035	5				1040
				1045	5				1050					1055	5
			1060)				1065	5	Pro			1070)	
		1075	5				1080)		Glu		1085	5		
	1090)				1095	5			Pro	1100)			
1105	5				1110)				Val 1115	5				1120
				1125	5				1130					1135	5
			1140)				1145	5	Val			1150)	_
		1155	5				1160)		Ser		1165	5		
	1170)				1175	5			Trp	1180)	_		_
1185	·)				1190)				Ser 1195	5				1200
				1205	5			_	1210		_	_		1215	5
Asp	Tyr	Pro	Gln 1220		Arg	Asp	Asn	Lys 1225		Arg	Ala	Glu	His 1230		Pro

Ser Gly Pro Leu Arg Gln Arg Glu Glu Ser Glu Thr Arg Ser Glu Ser 1235 1240 1245 Ser Asp Phe Glu Val Val Pro Lys Arg Arg Gln Arg Gly Ser Glu 1250 1255 1260 Thr Asp Thr Asp Ser Glu Ile His Glu Ser Ala Ser Asp Lys Asp Ser 1265 1270 1275 1280 Leu Ser Lys Gly Lys Leu Pro Lys Arg Glu Glu Arg Pro Glu Asn Lys 1285 1290 1295 Lys Pro Val Lys Pro His Ser Ser Phe Lys Pro Asp Asn His Val Arg 1300 1305 1310 Ile Asp Asn Arg Leu Leu Glu Lys Pro Tyr Val Arg Asp Asp Lys 1315 1320 1325 Ala Lys Pro Gly Phe Leu Pro Lys Gly Glu Pro Thr Arg Arg Gly Arg 1330 1335 1340 Gly Gly Thr Phe Arg Arg Gly Gly Arg Asp Pro Gly Gly Arg Pro Ser 1345 1350 1355 1360 Arg Pro Ser Thr Leu Arg Arg Pro Ala Tyr Arg Asp Asn Gln Trp Asn 1365 1370 1375 Pro Arg Gln Ser Glu Val Pro Lys Pro Glu Asp Gly Glu Pro Pro Arg 1380 1385 1390 Arg His Glu Gln Phe Ile Pro Ile Ala Ala Asp Lys Arg Pro Pro Lys 1395 1400 1405 Phe Glu Arg Lys Phe Asp Pro Ala Arg Glu Arg Pro Arg Arg Gln Arg 1410 1415 1420 Pro Thr Arg Pro Pro Arg Gln Asp Lys Pro Pro Arg Phe Arg Arg Leu 1425 1430 1435 Arg Glu Arg Glu Ala Ala Ser Lys Ser Asn Glu Val Val Ala Val Pro 1445 1450 1455 Thr Asn Gly Thr Val Asn Asn Val Ala Gln Glu Pro Val Asn Thr Leu 1460 1465 1470 Gly Asp Ile Ser Gly Asn Lys Thr Pro Asp Leu Ser Asn Gln Asn Ser 1475 1480 1485 Ser Asp Gln Ala Asn Glu Glu Trp Glu Thr Ala Ser Glu Ser Ser Asp 1490 1495 1500 Phe Asn Glu Arg Arg Glu Arg Asp Glu Lys Lys Asn Ala Asp Leu Asn 1510 1515 Ala Gln Thr Val Val Lys Val Gly Glu Asn Val Leu Pro Pro Lys Arg 1525 1530 1535 Glu Ile Ala Lys Arg Ser Phe Ser Ser Gln Arg Pro Val Asp Arg Gln 1540 1545 1550 Asn Arg Arg Gly Asn Asn Gly Pro Pro Lys Ser Gly Arg Asn Phe Ser 1555 1560 1565 Gly Pro Arg Asn Glu Arg Arg Ser Gly Pro Pro Ser Lys Ser Gly Lys 1570 1575 1580 Arg Gly Pro Phe Asp Asp Gln Pro Ala Gly Thr Thr Gly Val Asp Leu 1585 1590 1595 Ile Asn Gly Ser Ser Ala His His Gln Glu Gly Val Pro Asn Gly Thr 1605 1610 Gly Gln Lys Asn Ser Lys Asp Ser Thr Gly Lys Lys Arg Glu Asp Pro 1620 1625 1630 Lys Pro Gly Pro Lys Lys Pro Lys Glu Lys Val Asp Ala Leu Ser Gln 1635 1640 1645 Phe Asp Leu Asn Asn Tyr Ala Ser Val Val Ile Ile Asp Asp His Pro 1655 1660 Glu Val Thr Val Ile Glu Asp Pro Gln Ser Asn Leu Asn Asp Asp Gly 1670 1675 Phe Thr Glu Val Val Ser Lys Lys Gln Gln Lys Arg Leu Gln Asp Glu 1685

1690

Glu Arg Arg Lys Lys Glu Glu Gln Val Ile Gln Val Trp Asn Lys Lys

WO 02/101075 PCT/US02/18638

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Asn Ala Asn Glu 1715			r Ser Lys Leu 172	Pro Pro Arg
Phe Ala Lys Lys 1730			n Gln Ala Gln 1740	Ser Ser Ala
Ser Val Pro Pro 1745		Ala Pro Le		Thr Ser Ala 1760
Ser Val Pro Ala	Ser Thr Ser 1765	Ala Pro Le 17		
Val Pro Ala Ser 178				
Val Leu Ala Ser 1795			o Ala Ser Pro 180	Leu Ala Pro
Val Ser Ala Ser 1810	Ala Ser Val	Ser Ala Se		
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Thr Pro Ile Leu			o Ala Ser Val	-
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Ala Pro Thr Pro			r Pro Ala Ala 188	Pro Val Ile
Thr Ala Pro Thr 1890	Ile Pro Ala 189	Ser Ala Pr	o Thr Ala Ser	
Ala Pro Ala Ser 1905				Pro Val Ser 1920
Ala Pro Asn Pro	Ala Pro Pro 1925	Ala Pro Al 19	a Gln Thr Gln	
His Lys Pro Val	Gln Asn Pro			
Gln Pro Pro Pro 1955	Ser Ile Arg	Leu Pro Se 1960	r Ala Gln Thr 196	Pro Asn Gly
Thr Asp Tyr Val	Ala Ser Gly	Lys Ser Il 5	e Gln Thr Pro 1980	Gln Ser His
Gly Thr Leu Thr 1985	Ala Glu Leu 1990	Trp Asp As	n Lys Val Ala	Pro Pro Ala 2000
Val Leu Asn Asp	Ile Ser Lys 2005	Lys Leu Gl 20	y Pro Ile Ser	
Pro Pro Ser Val				
Ala Pro Ser Ser 2035	Glu Gly Ala	Lys Asn Gl 2040	y Gln Glu Ser 204	
Ile Gly Thr Asp 2050	Thr Ile Gln 205			
Glu Asn Glu Val 2065	. Val Pro Val 2070	Leu Ser Gl	u Lys Ser Ala 2075	Asp Lys Ile 2080
Pro Glu Pro Lys	Glu Gln Arg 2085	Gln Lys Gl		
Lys Ala Gln Lys 210	Leu Pro Asp	Leu Ser Pr 2105	o Val Glu Asn	
Lys Pro Gly Pro 2115	lle Gly Lys	Glu Arg Se 2120	r Leu Lys Asn 212	Arg Lys Val
Lys Asp Ala Glr 2130	Gln Val Glu 213	Pro Glu Gl		
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Pro Lys Arg Glu Thr Ile Gln Gln Ser Ser Leu Thr Ser Val Pro 2225 2230 2235 2240

Pro Thr Thr Phe Ser Leu Thr Phe Lys Met Glu Ser Ala Arg Lys Ala 2245 2250 2255

Trp Glu Asn Ser Pro Asn Val Arg Glu Lys Gly Ser Pro Val Thr Ser 2260 2265 2270

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Tyr Thr Thr Ser Ser Leu Ser Thr Lys Ser Thr Thr Thr Ser Asp Pro 2325 2330 2335

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Gln Pro Gly Leu Ser Gln Pro Thr Ser Val Gln Gln Ile Pro Ile Pro 2420 2425 2430

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Gln Ala Ser Gly Leu Gly Gly Ser Gln Leu Ile Asp Thr His Leu Leu 2530 2535 2540

Gln Ala Arg Ala Asn Leu Thr Gln Ala Ser Asn Leu Tyr Ser Gly Gln 2545 2550 2555

Val Gln Gln Pro Gly Gln Thr Asn Phe Tyr Asn Thr Ala Gln Ser Pro 2565 2570 2575

Ser Ala Leu Gln Gln Val Thr Val Pro Leu Pro Ala Ser Gln Leu Ser 2580 2585

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Leu Lys Lys Ser Asn Ala Pro Leu Val Asn Val Thr Leu Tyr Tyr Glu
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Leu Asp Glu Leu Asp Met Glu Leu Ala Phe Leu Thr Met Ser Gly Met
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Gly Gly Pro Arg His Ala Ala His Ala Arg Gln Arg Pro Ala Asp Arg
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Cys Ser Pro Ala Thr Ala Arg Val Cys Ala Leu Gly His Arg Gln Trp
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Glu Thr Leu Gly Arg Ser Asp Pro Ala Pro Tyr Pro Cys Leu Pro Val
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Ser Glu Thr Ser Val Pro Asp His Val Val Trp Ser Leu Phe Asn Thr
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WO 02/101075 PCT/US02/18638

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250

WO 02/101075 PCT/US02/18638

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Tyr Gly Asn Gly Val Pro Glu Ser Ser Arg Ala Ser Leu Lys Cys Tyr
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Arg 305	Ala	Thr	Gln	Ser	Ala 310	Lys	Glu	Leu	Asp	Val 315	Lys	Ile	Lys	Asn	Val 320
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Glu	Gly	Asn	Asn 340	Val	Pro	Ser	Gly	Asp 345	Phe	Ser	Arg	Glu	Trp 350	Ala	Glu
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Val	Pro 770	Met	Arg	Phe	Asn	Gly 775		Ser	Gly	Val	Glu 780		Arg	Leu	Pro
Asn 785	Asp	Leu	Glu	Asp	Leu 790		Gly	Туг	Thr	Ser 795	-	Ser	Leu	Phe	Leu 800
	Arg	Pro	Asn	Ser 805		Glu	Asn	Gly	Gly 810	Thr	Glu	Asn	Met	Phe 815	
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1025	5				1030)				Met 1035	5				1040
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	1090)				1095	5			Ile	1100)			
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1185	5				1190)			-	Asn 1195	5				1200
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Ile Glu Pro Ala Pro Pro Ser Gln Gly Ala Glu Ala Lys Gly Glu Val
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755 760 765
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790

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Thr Gln Arg Ile Arg Cys Arg Val Pro Cys Asn Trp Lys Lys Glu Phe
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Gly Ala Asp Cys Lys Tyr Lys Phe Glu Asn Trp Gly Ala Cys Asp Gly
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410

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WO 02/101075 PCT/US02/18638 199

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-				405					410					Arg 415	
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201

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203

Ser	Glu	Arg 275	Leu	Tyr	Thr	Arg	Asp 280	Gly	Asn	Ala	Asp	Gly 285	Lys	Pro	Cys
Gln	Phe 290	Pro	Phe	Ile	Phe	Gln 295	Gly	Gln	Ser	Tyr	Ser 300	Ala	Cys	Thr	Thr
A <i>s</i> p 305	Gly	Arg	Ser	Asp	Gly 310	Tyr	Arg	Trp	Cyś	Ala 315	Thr	Thr	Ala	Asn	Tyr 320
Asp	Arg	Asp	Lys	Leu 325	Phe	Gly	Phe	Суѕ	Pro 330	Thr	Arg	Ala	Asp	Ser 335	Thr
Val	Met	Gly	Gly 340	Asn	Ser	Ala	Gly	Glu 345	Leu	Суѕ	Val	Phe	Pro 350	Phe	Thr
Phe	Leu	Gly 355	Lys	Glu	Tyr	Ser	Thr 360	Cys	Thr	Ser	Glu	Gly 365	Arg	Gly	Asp
	370					375					380		Asp		
Trp 385	Gly	Phe	Cys	Pro	Asp 390	Gln	Gly	Tyr	Ser	Leu 395	Phe	Leu	Val	Ala	Ala 400
His	Glu	Phe	Gly	His 405	Ala	Leu	Gly	Leu	Asp 410	His	Ser	Ser	Val	Pro 415	Glu
			420				_	425			_		Pro 430		
		435					440			_		445	Arg		
	450					455					460		Thr		
465					470	_				475			Ser		480
				485					490				Thr	495	
			500					505					Ser 510		
		515					520					525	Glu		_
	530					535					540		Phe		
545					550					555			Asp		560
				565					570				Pro	575	
			580					585					Tyr 590		_
		595					600					605	Leu Gly		
	610					615					620		Lys		
625					630					635			Phe		640
		-		645					650	-	_			655	_
			660					665					Lys 670		
		675					680					685	Ser Leu		
	690 Glu		2100	0,111	v u.i.	695	т Х т	val	T11T	т Х т	700	**C	ъсц	2711	Cys
705	Jiu	110 D													

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Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu 85 90 Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro 105 Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Phe Leu Asn Pro 120 Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile 135 Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln 150 155 Arg Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu 165 170 Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu 180 185 Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu 200 205 Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg 215 220 Ala Ala Leu Gln Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp 230 235 240 Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly 245 250 255 Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg 260 265 270 Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile 275 280 Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser 295 300 Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys 310 315 Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met 325 330 335 Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu 345 350 Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val 355 360 365 Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile 375 380 Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu 390 395 Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Pro Leu 405 410 Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln 420 425 Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr 435 440 Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser 455 Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln 470 475 Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn 485 490 Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro 500 505 Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu 520 Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val 535 Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala

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545
                    550
                                         555
Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
                565
                                     570
Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
            580
                                585
                                                     590
Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Gly Gly Arg Gly Gln
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                                                 605
Ala Arg Ala Gly Gly Arg Ala Gly Gly Val Glu Val Gly Ala Leu Ser
                        615
                                             620
His Pro Ser Leu Cys Arg Gly Pro Leu Gly Asp Ala Leu Pro Pro Arg
                    630
                                         635
Thr Trp Thr Cys Ser His Arg Pro Gly Thr Ala Pro Ser Leu His Pro
                645
                                     650
Gly Leu Arg Ala Pro Leu Pro Cys Trp Pro Gln Pro Cys Trp Gly Ser
            660
                                665
Pro Pro Gly Gln Glu Gln Ala Arg Val Ile Pro Val Pro Pro Gln Glu
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Asn Ser Arg Ser Val Asn Gly Asn Met Pro Pro Ala Asp Thr
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<210> 145 <211> 2135 <212> DNA <213> Homo sapiens

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ctaggacctg gacctgttct caccgtcctg gcactgctcc tagcctccac cctggcctga 1980 gggccccact cccttgctgg ccccagccct gctggggatc cccgcctggc caggagcagg 2040 cacgggtgat ccccgttcca ccccaagaga actcgcgctc agtaaacggg aacatgccc 2100 ctgcagacac gtaaaaaaaa aaaaaaaaa aaaaa

<210> 146 <211> 630 <212> PRT

<213> Homo sapiens

<400> 146 Met Ala Leu Pro Thr Ala Arg Pro Leu Gly Ser Cys Gly Thr Pro 1.0 Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln 2.5 Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu 40 Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg 55 Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu 70 75 Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu 85 90 Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro 105 Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Phe Leu Asn Pro 120 Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile 135 Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln 150 155 Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu 165 170 Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu 185 Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu 200 Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg 215 Ala Ala Leu Gln Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp 230 235 Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly 250 Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg 265 Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile 280 Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser 295 300 Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys 310 315 Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met 325 330 Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu 345 Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val 360 Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile 375

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Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385
                    390
                                        395
Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Pro Leu
                405
                                    410
                                                         415
Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln
            420
                                425
Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
        435
                            440
                                                 445
Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser
                        455
                                            460
Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
                    470
                                        475
Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
                485
                                    490
                                                         495
Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
                                505
                                                     510
Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
                            520
                                                525
        515
Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
                        535
                                            540
Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala
                    550
                                        555
Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
                565
                                    570
                                                        575
Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
                                585
                                                    590
Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Glu Ala Leu Ser Gly Thr
                            600
                                                605
Pro Cys Leu Leu Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu Leu
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Leu Ala Ser Thr Leu Ala
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<210> 147
<211> 2105
<212> DNA
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<213> Homo sapiens

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<210> 148

<211> 620

<212> PRT

<213> Homo sapiens

<400> 148

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210

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Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
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Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
               325
                                  330
Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
                               345
Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
                           360
Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
                       375
Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
                   390
                                      395
Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu
               405
                                 410
Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln
                              425
           420
                                                  430
Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
                          440
                                              445
       435
Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser
                       455
                                      460
Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
                                      475
                   470
Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
               485
                                  490
Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
                              505
                                                  510
Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
                          520
                                              525
       515
Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
                       535
                                          540
Ala Glu Val Gln Lys Leu Gly Pro His Val Glu Gly Leu Lys Ala
                   550
                                      555
Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
               565
                                  570
Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
                          585
Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Gly Pro Gly Pro Val Leu
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Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala
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<210> 149

<211> 2193

<212> DNA

<213> Homo sapiens

<400> 149

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PCT/US02/18638

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Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His
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Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro
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PCT/US02/18638

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Ala	Pro	Asp	Thr	Arg 165	Pro	Ala	Pro	Gly	Ser 170	Thr	Ala	Pro	Pro	Ala 175	His
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Pro	Pro	Ala 195	His	Gly	Val	Thr	Ser 200	Ala	Pro	Asp	Thr	Arg 205	Pro	Ala	Pro
Gly	Ser 210	Thr	Ala	Pro	Pro	Ala 215	Hís	Gly	Val	Thr	Ser 220	Ala	Pro	Asp	Thr
Arg 225	Pro	Ala	Pro	Gly	Ser 230	Thr	Ala	Pro	Pro	Ala 235	His	Gly	Val	Thr	Ser 240
Ala	Pro	Asp	Thr	Arg 245	Pro	Ala	Pro	Gly	Ser 250	Thr	Ala	Pro	Pro	Ala 255	His
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222

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		835					840			Thr		845			
	850					855				Ala	860				
865					870					875 Thr					880
				885					890	Ala				895	
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	1010)				1015	5			Gln	1020)			
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PCT/US02/18638

223

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Arg	Gln 450	Gly	Ala	Ser	Phe	Leu 455	Gly	Ile	Leu	Asp	Ile 460	Ala	Gly	Phe	Glu
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	Gln Lys			725		-			730					735	
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1235

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Lys Val His Lys Leu Gln Asn Glu Val Glu Ser Val Thr Gly Met Leu
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1330

Arg Asn Ser Leu Gln Asp Gln Leu Asp Gln Glu Met Glu Ala Lys Gln
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WO 02/101075 PCT/US02/18638 233

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Val	Gly	Ala	Asn 260	Ile	Glu	Thr	Tyr	Leu 265	Leu	Glu	Lys	Ser	Arg 270	Ala	Ile
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			Gln	565					570					575	
			Tyr 580					585					590		
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	610		Asp -			615		_		_	620				
625			Leu		630					635					640
			Lys	645	-	_	_		650	_			_	655	
			Gln 660					665					670		
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PCT/US02/18638 **WO** 02/101075

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Gln Ser Lys C 1265	1270	-	1275		1280
Lys Val His L	1285	1	290	_	1295
	.300	1305		1310)
Leu Ser Ser G 1315		1320		1325	
Arg Gln Lys L 1330	1:	335	1340	ı	•
Arg Asn Ser L 1345	1350		1355		1360
Asn Leu Glu A	1365	1	370		1375
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                             25
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Val Ser Ala Cys Asp Thr Glu Asp Thr Val Gly His Leu Gly Pro Trp
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Arg Asp Lys Asp Pro Ala Leu Trp Cys Gln Leu Cys Leu Ser Ser Gln
                     55
                                        60
His Gln Ala Ile Glu Arg Phe Tyr Asp Lys Met Gln Asn Ala Glu Ser
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                                    75
Gly Arg Gly Gln Val Met Ser Ser Leu Ala Glu Leu Glu Asp Asp Phe
              85
                                 90
Lys Glu Gly Tyr Leu Glu Thr Val Ala Ala Tyr Tyr Glu Glu Gln His
           100
                             105
Pro Glu Leu Thr Pro Leu Leu Glu Lys Glu Arg Asp Gly Leu Arg Cys
       115
                         120
                                           125
Arg Gly Asn Arg Ser Pro Val Pro Asp Val Glu Asp Pro Ala Thr Glu
                     135
                                        140
Glu Pro Gly Glu Ser Phe Cys Asp Lys Val Met Arg Trp Phe Gln Ala
                  150
                                    155
Met Leu Gln Arg Leu Gln Thr Trp Trp His Gly Val Leu Ala Trp Val
              165
                                170
Lys Glu Lys Val Val Ala Leu Val His Ala Val Gln Ala Leu Trp Lys
           180
                             185
Gln Phe Gln Ser Phe Cys Cys Ser Leu Ser Glu Leu Phe Met Ser Ser
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Phe Gln Ser Tyr Gly Ala Pro Arg Gly Asp Lys Glu Glu Leu Thr Pro
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Gln Lys Cys Ser Glu Pro Gln Ser Ser Lys
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<212> DNA
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gctgataaat agtttatacc caccaggaca agagcccata cccaagatct cagagtcaaa 300
gatggctttt aagcagatgg agcaaatctc ccagttccta aaagctgcgg agacctatgg 360
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<210> 170 <211> 282 <212> PRT

<213> Homo sapiens

<400> 170

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<210> 171

<211> 942

<212> DNA

<213> Homo sapiens

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gccacatggc taaaccctga cccatctcag aagcagaatc tcctagcccc acagaatgct 180
gtgtcctctg aagaaaccaa tgactttaaa caagagaccc ttccaagtaa gtccaacgaa 240
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gactccattg actcgaacga ctctgatgat gtagatgaca ctgatgattc tcaccagtct 360
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ccagcaaccg aagttttcac tccagttgtc cccacagtag acacatatga tggccgaggt 480
gatagtgtgg tttatggact gaggtcaaaa tctaagaagt ttcgcagacc tgacatccag 540
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gcatacaagg ccatccccgt tgcccaggac ctgaacgcgc cttctgattg ggacagccgt 660
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aagcagtcca gattatataa geggaaagct aatgatgaga geaatgagca tteegatgtg 780
attgatagtc aggaactttc caaagtcagc cgtgaattcc acagccatga atttcacagc 840
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<212> PRT
<213> Homo sapiens
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                                25
Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
                            40
Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Asn Ala Val Ser Ser Glu
Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro Ser Lys Ser Asn Glu
                    70
                                        75
Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp His
                                    90
Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp Val Asp
                                105
Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser Asp Glu
                            120
                                                125
Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala Thr Glu
                        135
                                            140
Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly Arg Gly
                    150
                                        155
                                                            160
Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe Arg Arg
                165
                                    170
                                                        175
Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu His Ile Thr Ser His
                                185
Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro Val Ala
                            200
Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys Asp Ser
                        215
                                            220
Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Ala His Ser His
                    230
                                        235
Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser Asn Glu
                                    250
His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser Arg Glu
            260
                                265
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Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val Val Asp 275 280 Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile Ser His 295 300 Glu Leu Asp Ser Ala Ser Ser Glu Val Asn 310 <210> 173 <211> 1524 <212> DNA <213> Homo sapiens <400> 173 qcagagcaca gcatcgtcgg gaccagactc gtctcaggcc agttgcagcc ttctcagcca 60 aacgccgacc aaggaaaact cactaccatg agaattgcag tgatttgctt ttgcctccta 120 ggcatcacct gtgccatacc agttaaacag gctgattctg gaagttctga ggaaaagcag 180 ctttacaaca aatacccaqa tgctqtqqcc acatqqctaa accctqaccc atctcaqaaq 240 cagaatctcc tagccccaca gacccttcca agtaagtcca acgaaagcca tgaccacatg 300 gatgatatgg atgatgaaga tgatgatgac catgtggaca gccaggactc cattgactcg 360 aacgactctg atgatgtaga tgacactgat gattctcacc agtctgatga gtctcaccat 420 tctgatgaat ctgatgaact ggtcactgat tttcccacgg acctgccagc aaccgaagtt 480 ttcactccag ttgtccccac agtagacaca tatgatggcc gaggtgatag tgtggttrat 540 ggactgaggt caaaatctaa gaagtttcgc agacctgaca tccagtaccc tgatgctaca 600 gacgaggaca tcacctcaca catggaaagc gaggagttga atggtgcata caaggccatc 660 cccgttgccc aggacctgaa cgcgccttct gattgggaca gccgtgggaa ggacagttat 720 gaaacgagtc agctggatga ccagagtgct gaaacccaca gccacaagca gtccagatta 780 tataaqcgga aagccaatga tgagagcaat gagcattccg atgtgattga tagtcaggaa 840 ctttccaaag tcagccgtga attccacagc catgaatttc acagccatga agatatgctg 900 qttqtaqacc ccaaaaqtaa qgaaqaaqat aaacacctga aatttcgtat ttctcatgaa 960 ttagatagtg catcttctga ggtcaattaa aaggagaaaa aatacaattt ctcactttgc 1020 atttagtcaa aagaaaaaat getttatage aaaatgaaag agaacatgaa atgettettt 1080 ctcagtttat tggttgaatg tgtatctatt tgagtctgga aataactaat gtgtttgata 1140 attagtttag tttgtggctt catggaaact ccctgtaaac taaaagcttc agggttatgt 1200 ctatgttcat tctatagaag aaatgcaaac tatcactgta ttttaatatt tgttattctc 1260 tcatgaatag aaatttatgt agaagcaaac aaaatacttt tacccactta aaaagagaat 1320 ataacatttt atgtcactat aatcttttgt tttttaagtt agtgtatatt ttgttgtgat 1380 tatctttttq tqgtgtgaat aaatctttta tcttgaatgt aataagaatt tggtggtgtc 1440 aattgcttat ttgttttccc acggttgtcc agcaattaat aaaacataac cttttttact 1500 gcctaaaaaa aaaaaaaaa aaaa <210> 174 <211> 300 <212> PRT <213> Homo sapiens <400> 174 Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu 25 20 Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro 40 Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Thr Leu Pro Ser Lys Ser 55 Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp 70 75 Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp 90

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Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser
            100
                                105
Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala
                            120
                                                125
Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly
                        135
Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe
                    150
                                        155
Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu Asp Ile Thr
                                    170
                                                        175
Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro
                                185
                                                    190
Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys
                            200
                                                205
Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His
                        215
                                            220
Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser
                    230
                                        235
Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser
                                    250
                245
Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val
            260
                                265
Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile
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                                                285
Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
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<212> DNA

<213> Homo sapiens

<400> 175

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gactttaaac aagagaccct tccaagtaag tccaacgaaa gccatgacca catggatgat 180
atggatgatg aagatgatga tgaccatgtg gacagccagg actccattga ctcgaacgac 240
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gaatctgatg aactggtcac tgattttccc acggacctgc cagcaaccga agttttcact 360
ccagttgtcc ccacagtaga cacatatgat ggccgaggtg atagtgtggt ttatggactg 420
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aaagtcagcc gtgaattcca cagccatgaa tttcacagcc atgaagatat gctggttgta 780
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<210> 176

<211> 287 <212> PRT

<213> Homo sapiens

<400> 176

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Ser Lys Ser Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu
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Asp Asp Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp
                    70
                                        75
Ser Asp Asp Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser
                                    90
His His Ser Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp
            100
                                105
                                                    110
Leu Pro Ala Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr
        115
                            120
                                                125
Tyr Asp Gly Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser
                        135
                                            140
Lys Lys Phe Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu
                    150
                                        155
His Ile Thr Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys
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                                    170
                                                        175
Ala Ile Pro Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser
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                                185
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Arg Gly Lys Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala
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                                                205
Glu Ala His Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn
                        215
                                            220
Asp Glu Ser Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser
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                                        235
Lys Val Ser Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp
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                                   250
Met Leu Val Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys
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<210> 177 <211> 3213
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<212> DNA

<213> Homo sapiens

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                                25
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Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr
                        55
Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
                    70
                                        75
                                                            80
Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu
                                    90
Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr
                                105
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Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly 120

T.170	Gly	Ser	Phe	Thr	ጥኣ፣ንግ	Phe	ב וֹ ע	Dro	Sor	7\ = D	Glu.	ת דית	Trn	7 en	7) S.D.
	130					135					140				
Leu 145	Asp	Ser	Asp	Ile	Arg 150	Arg	Gly	Leu	Glu	Ser 155	Asn	Val	Asn	Val	Glu 160
Leu	Leu	Asn	Ala	Leu 165	His	Ser	His	Met	Ile 170	Asn	Lys	Arg	Met	Leu 175	Thr
Lys	Asp	Leu	Lys 180		Gly	Met	Ile	Ile 185		Ser	Met	Tyr	Asn 190	Asn	Leu
Gly	Leu	Phe 195		Asn	His	Tyr	Pro 200		Gly	Val	Val	Thr 205		Asn	Cys
Ala	Arg 210	Ile	Ile	His	Gly	Asn 215	Gln	Ile	Ala	Thr	Asn 220	Gly	Val	Val	His
Val 225	Ile	Asp	Arg	Val	Leu 230	Thr	Gln	Ile	Gly	Thr 235	Ser	Ile	Gln	Asp	Phe 240
	Glu	Ala	Glu	Asp 245		Leu	Ser	Ser	Phe 250		Ala	Ala	Ala	Ile 255	
Ser	Asp	Ile	Leu 260		Ala	Leu	Gly	Arg 265		Gly	His	Phe	Thr 270		Phe
Ala	Pro	Thr 275		Glu	Ala	Phe	Glu 280	_	Leu	Pro	Arg	Gly 285		Leu	Glu
Arg	Phe 290		Gly	Asp	Lys	Val 295		Ser	Glu	Ala	Leu 300		Lys	Tyr	\mathtt{His}
Ile 305	Leu	Asn	Thr	Leu	Gln 310		Ser	Glu	Ser	Ile 315		Gly	Gly	Ala	Val 320
	Glu	Thr	Leu	Glu 325		Asn	Thr	Ile	Glu 330		Gly	Cys	Asp	Gly 335	-
Ser	Ile	Thr	Val 340		Gly	Ile	Lys	Met 345		Asn	Lys	Lys	Asp 350		Val
Thr	Asn	Asn 355	Gly	Val	Ile	His	Leu 360	Ile	Asp	Gln	Val	Leu 365	Ile	Pro	Asp
Ser	Ala 370	Lys	Gln	Val	Ile	Glu 375		Ala	Gly	Lys	Gln 380		Thr	Thr	Phe
Thr 385	Asp	Leu	Val	Ala	Gln 390	Leu	Gly	Leu	Ala	Ser 395	Ala	Leu	Arg	Pro	Asp 400
Gly	Glu	Tyr	Thr	Leu 405	Leu	Ala	Pro	Val	Asn 410		Ala	Phe	Ser	Asp 415	Asp
Thr	Leu	Ser	Met 420	Val	Gln	Arg	Leu	Leu 425	Lys	Leu	Ile	Leu	Gln 430	Asn	His
Ile	Leu	Lys 435	Val	Lys	Val	Gly	Leu 440	Asn	Glu	Leu	Tyr	Asn 445	Gly	Gln	Ile
Leu	Glu 450	Thr	Ile	Gly	Gly	Lys 455	Gln	Leu	Arg	Val	Phe 460	Val	Tyr	Arg	Thr
Ala 465	Val	Cys	Ile	Glu	Asn 470	Ser	Cys	Met	Glu	Lys 475	Gly	Ser	Lys	Gln	Gly 480
Arg	Asn	Gly	Ala	Ile 485	His	Ile	Phe	Arg	Glu 490	Ile	Ile	Lys	Pro	Ala 495	Glu
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Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
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                                        75
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Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr
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155

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135

1.50

115

WO 02/101075 PCT/US02/18638

Leu	Leu	Asn	Ala	Leu 165	His	Ser	His	Met	Ile 170	Asn	Lys	Arg	Met	Leu 175	Thr
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Gly	Leu	Phe 195	Ile	Asn	Hìs	Тух	Pro 200	Asn	Gly	Val	Val	Thr 205	Val	Asn	Cys
Ala	Arg 210	Ile	Ile	His	Gly	Asn 215	Gln	Ile	Ala	Thr	Asn 220	Gly	Val	Val	His
Val 225	Ile	Asp	Arg	Val	Leu 230	Thr	Gln	Ile	Gly	Thr 235	Ser	Ile	Gln	Asp	Phe 240
Ile	Glu	Ala	Glu	Asp 245	Asp	Leu	Ser	Ser	Phe 250	Arg	Ala	Ala	Ala	Ile 255	Thr
Ser	Asp	Ile	Leu 260	Glu	Ala	Leu	Gly	Arg 265	Asp	Gly	His	Phe	Thr 270	Leu	Phe
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	Ala 370					375			_	_	380				
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	Glu			405					410					415	
	Leu		420					425					430		
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	Glu 450					455					460				
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	Glu		580					585					590		
	Phe	595					600					605			_
	Lys 610					615					620				
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<211> 2304

<212> DNA

<213> Homo sapiens

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His Trp Cys Asn Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile
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Asp Lys Ser Lys Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly
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Glu Cys Met Val His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro
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Pro Glu Glu Leu Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg
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Phe Lys Ile Ile Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp
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Cys Gly Gly Ser Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His
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Arg Ser Arg Leu Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val
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Glu Asn Leu Ile Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His
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His Asn Asp Ile Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys
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Ala Gln Pro Ser Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr
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Asn Asp Pro Gln Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys
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Val Lys Leu Ile Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly
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Ser Glu Val Thr Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys
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Gln Gly Arg Met Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys
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<211> 2123

<212> DNA

<213> Homo sapiens

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<212> PRT

<213> Homo sapiens

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Gly Lys Ile Val Pro Lys Ser Leu Leu Lys Pro His Gln Arg Glu
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	Pro			325					330			_		335	
	Lys		340					345					350		
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	Ser		420					425			_	_	430		
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	Ser 450					455					460				
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	Thr		500					505					510		
	Trp	515					520					525			_
	Val 530					535		_			540				_
545	Leu				550					555					560
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<213> Homo sapiens

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 Glu
 Leu
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 Lys
 Ala
 Lys

 Glu
 Ser
 Leu
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 Asn
 Val
 Asp
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 Ile
 Arg
 Lys
 Leu
 Thr
 Gly
 Arg

 Asp
 Pro
 Asn
 Asp
 Val
 Arg
 Pro
 Ile
 Gln
 Ala
 Arg
 Leu
 Leu
 Ala
 Leu
 Ser

 Gly
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 Ser
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 Leu
 Leu
 Arg
 Gly

 Gly
 Pro
 Gly
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 Arg
 Gly
 Ser
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 Leu
 Arg
 Gly

WO 02/101075 PCT/US02/18638

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Glu	Leu	Phe 195	Glu	Glu	Arg	Arg	Ala 200	Lys	Gln	Thr	Glu	Leu 205	Arg	Leu	Leu
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225					230					235		Lys			240
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		355			_		360				_	Met 365			
	370		_			375	-			_	380	Gln			
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			420					425				Glu	430		
		435					440					Lys 445			
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Ser 465	Glu	Pro	Gln	Pro	Glu 470	Pro	Val	Ala	Gln	Pro 475	Gln	Ala	Gln	Ser	Gln 480
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			500					505				Gln	510		
Gln	Ser	Gln 515	Cys	His	Ala	Val	Leu 520	Gln	Ser	His	Pro	Pro 525	Ser	Gln	Pro
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<212> PRT

WO 02/101075 PCT/US02/18638

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WO 02/101075 PCT/US02/18638

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Lys Ser Ile Gln Asp Leu Arg Arg Phe Phe Leu His His Leu Ile
Ala Glu Ile His Thr Ala Glu Ile Arg Ala Thr Ser Glu Val Ser Pro
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Asn Ser Lys Pro Ser Pro Asn Thr Lys Asn His Pro Val Arg Phe Gly
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Ser Asp Asp Glu Gly Arg Tyr Leu Thr Gln Glu Thr Asn Lys Val Glu
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Thr Tyr Lys Glu Gln Pro Leu Lys Thr Pro Gly Lys Lys Lys Gly
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lys Pro Gly Lys Arg Lys Glu Gln Glu Lys Lys Lys Arg Arg Thr Arg
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	Arg		580					585				_	590		
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	Ala		660					665				_	670		
	Leu	675					680					685			
	Gln 690					695					700				
705	Thr				710		_	_		715					720
	Ser			725					730	-				735	
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	Asp			805					810					815	
	Leu		820					825					830		
	Gln -	835					840					845			
	Leu 850					855					860				
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WO 02/101075 PCT/US02/18638

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Ser Val Phe Ser Val Leu Ser Asn Ser Ala Glu Val Lys Arg Gly Arg
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Leu Glu Asp Val Val Gly Gly Cys Cys Tyr Arg Val Asn Asn Ser Leu
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Asp His Glu Tyr Gln Pro Arg Pro Val Glu Val Ile Ile Ser Ser Ala
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Lys Glu Met Val Gly Gln Lys Met Lys Tyr Ser Ile Val Ser Arg Asn
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Gln Val Glu Lys Ala Lys Val Glu Val Gly Val Ala Thr Ala Leu Gly
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His Met Ile Ile Arg Thr Leu Ser Thr Phe Arg Asn Tyr Ile Met Asp
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Val Gln Lys Gly Glu Lys Glu Gly Arg Gly Trp Thr Gln Trp Ile Glu
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Gln Thr Ala Thr Ala Thr Cys Phe Asp Ala Ala Gln Gly Lys Thr Arg 150 155 Thr Leu Met Glu Lys Asp Ser Tyr Pro Arg Phe Leu Lys Ser Pro Ala 170

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<211> 303

<212> PRT

<213> Homo sapiens

<400> 210

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Tyr Ile Gly Pro Cys Lys Tyr Ile Pro Pro Cys Leu Asp Ser Glu Leu
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Thr Glu Phe Pro Leu Arg Met Arg Asp Trp Leu Lys Asn Val Leu Val
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                                                         175
Thr Leu Tyr Glu Arg Asp Glu Asp Asn Asn Leu Leu Thr Glu Lys Gln
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Lys Leu Arg Val Lys Lys Ile His Glu Asn Glu Lys Arg Leu Glu Ala
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Gly Asp His Pro Val Glu Leu Leu Ala Arg Asp Phe Glu Lys Asn Tyr
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Asn Met Tyr Ile Phe Pro Val His Trp Gln Phe Gly Gln Leu Asp Gln
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His Pro Ile Asp Gly Tyr Leu Ser His Thr Glu Leu Ala Pro Leu Arg
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                                    250
Ala Pro Leu Ile Pro Met Glu His Cys Thr Thr Arg Phe Phe Glu Thr
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Cys Asp Leu Asp Asn Asp Lys Tyr Ile Ala Leu Asp Glu Trp Ala Gly
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<213> Homo sapiens

<400> 212

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Pro His Ser Ser Asp Thr Glu Leu Pro Lys Asp Lys Leu Ser Ser Ala 325 330 335

Asp Asp His Arg Val Asn Ser Gly Phe Gly Arg Gly Leu Ser Asp Lys 340 345 350

Lys Ser Gly Glu Ser Gln Val Leu Phe Glu Thr Glu Ile Ser Arg Lys 355 360 365

Leu Phe Asp Thr Leu Asn Glu Asp Leu Phe Gln Lys Ile Leu Val Pro

370 375 380

Ile Gln Gln Val Leu Lys Glu Gly His Leu Glu Lys Thr Glu Ile Asp 385 390 395 400

Glu Val Val Leu Val Gly Gly Ser Thr Arg Ile Pro Arg Ile Arg Gln 405 410 415

Val Ile Gln Glu Phe Phe Gly Lys Asp Pro Asn Thr Ser Val Asp Pro 420 425 430

Asp Leu Ala Val Val Thr Gly Val Ala Ile Gln Ala Gly Ile Asp Gly 435 440 445

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25 Pro Val Thr Pro Ser Ala Leu Val Leu Met Ser Arg Ser Asn Val Gln 40 Pro Thr Ala Ala Pro Gly Gln Lys Val Met Glu Asn Ser Ser Gly Thr Pro Asp Ile Leu Thr Arg His Phe Thr Ile Asp Asp Phe Glu Ile Gly 75 Arg Pro Leu Gly Lys Gly Lys Phe Gly Asn Val Tyr Leu Ala Arg Glu 90 Lys Lys Ser His Phe Ile Val Ala Leu Lys Val Leu Phe Lys Ser Gln 105 110 Ile Glu Lys Glu Gly Val Glu His Gln Leu Arg Arg Glu Ile Glu Ile 115 120 125 Gln Ala His Leu His His Pro Asn Ile Leu Arg Leu Tyr Asn Tyr Phe 135 140 Tyr Asp Arg Arg Ile Tyr Leu Ile Leu Glu Tyr Ala Pro Arg Gly 150 155 Glu Leu Tyr Lys Glu Leu Gln Lys Ser Cys Thr Phe Asp Glu Gln Arg 165 170 Thr Ala Thr Ile Met Glu Glu Leu Ala Asp Ala Leu Met Tyr Cys His 180 185 Gly Lys Lys Val Ile His Arg Asp Ile Lys Pro Glu Asn Leu Leu Leu 200 205 Gly Leu Lys Gly Glu Leu Lys Ile Ala Asp Phe Gly Trp Ser Val His 215 220 Ala Pro Ser Leu Arg Arg Lys Thr Met Cys Gly Thr Leu Asp Tyr Leu 230 235 Pro Pro Glu Met Ile Glu Gly Arg Met His Asn Glu Lys Val Asp Leu 245 250

Val Ser Ala His Pro Trp Val Arg Ala Asn Ser Arg Arg Val Leu Pro 325 330 335

Pro Ser Ala Leu Gln Ser Val Ala 340

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<211> 1421

<212> DNA

<213> Homo sapiens

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Ser Thr Glu Leu Met Arg Arg Val Arg Arg Phe Gln Ile Ala Gln Tyr
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Lys Cys Leu Val Ile Lys Tyr Ala Lys Asp Thr Arg Tyr Ser Ser Ser
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Phe Cys Thr His Asp Arg Asn Thr Met Glu Ala Leu Pro Ala Cys Leu
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                                       7.5
Leu Arg Asp Val Ala Gln Glu Ala Leu Gly Val Ala Val Ile Gly Ile
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                                   90
Asp Glu Gly Gln Phe Pro Asp Ile Met Glu Phe Cys Glu Ala Met
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                           120
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Gln Arg Lys Pro Phe Gly Ala Ile Leu Asn Leu Val Pro Leu Ala Glu
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Ser Val Val Lys Leu Thr Ala Val Cys Met Glu Cys Phe Arg Glu Ala
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Ala Tyr Thr Lys Arg Leu Gly Thr Glu Lys Glu Val Glu Val Ile Gly
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Gly Ala Asp Lys Tyr His Ser Val Cys Arg Leu Cys Tyr Phe Lys Lys
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Pro Glu Gly Pro Ala Val Ala Val Arg Leu Ser Lys Asp Arg Ser Thr
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Asp Asn Phe Thr Glu Ala Leu Ala Glu Thr Ala Cys Arg Gln Met Gly
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Tyr Ser Ser Lys Pro Thr Phe Arg Ala Val Glu Ile Gly Pro Asp Gln
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Asp Leu Asp Val Val Glu Ile Thr Glu Asn Ser Gln Glu Leu Arg Met
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Arg Asn Ser Ser Gly Pro Cys Leu Ser Gly Ser Leu Val Ser Leu His
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Cys Leu Ala Cys Gly Lys Ser Leu Lys Thr Pro Arg Val Val Gly Gly
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Glu Glu Ala Ser Val Asp Ser Trp Pro Trp Gln Val Ser Ile Gln Tyr
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Asp Lys Gln His Val Cys Gly Gly Ser Ile Leu Asp Pro His Trp Val
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Leu Thr Ala Ala His Cys Phe Arg Lys His Thr Asp Val Phe Asn Trp
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Thr Val Arg Pro Ile Cys Leu Pro Phe Phe Asp Glu Glu Leu Thr Pro
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Gly Lys Met Ser Asp Ile Leu Leu Gln Ala Ser Val Gln Val Ile Asp
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<213> Homo sapiens

<400> 222

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Asp 65	Glu	Asp	Val	Gly	Ile 70	Asn	Tyr	Arg	Glu	Val 75	Thr	Phe	Val	Pro	Gly 80
Leu	Tyr	Lys	Ile	Phe 85	Asp	Glu	Ile	Leu	Val 90	Asn	Ala	Ala	Asp	Asn 95	Lys
Gln	Arg	Asp	Pro 100	Lys	Met	Ser	Cys	Ile 105	Arg	Val	Thr	Ile	Asp 110	Pro	Glu
Asn	Asn	Leu 115	Ile	Ser	Ile	Trp	Asn 120	Asn	Gly	Lys	Gly	Ile 125	Pro	Val	Val
Glu	His 130	Lys	Val	Glu	Lys	Met 135	Tyr	Val	Pro	Ala	Leu 140	Ile	Phe	Gly	Gln
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			Gly	165					170					175	
			Glu 180					185					190		
		195	Asp			-	200		_			205		_	
	210		Glu			215					220				
225		-	Met		230		_	_	_	235					240
			Tyr	2.45			_		250				_	255	
			Asn 260					265					270		
		275	Lys				280					285			
	290		Gln			295					300				
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			Arg	325					330					335	
			Val 340					345					350		
		355	Val				360					365			
	370		Thr			375					380				
385			Phe		390					395					400
			Gly	405					410					415	
			Gln 420					425					430		
		435	Lys				440					445	_		
	450		Ser			455					460		_	-	
465	_		Leu		470					475					480
туг	стЛ	va⊥	Phe	Pro 485	Leu	Arg	GТĀ	ьуѕ	11e 490	ьeu	Asn	Val	Arg	Glu 495	Ala

Ser His Lys Gln Ile Met Glu Asn Ala Glu Ile Asn Asn Ile Ile Lys 505 Ile Val Gly Leu Gln Tyr Lys Lys Asn Tyr Glu Asp Glu Asp Ser Leu 520 Lys Thr Leu Arg Tyr Gly Lys Ile Met Ile Met Thr Asp Gln Asp Gln 535 540 Asp Gly Ser His Ile Lys Gly Leu Leu Ile Asn Phe Ile His His Asn 545 550 555 560 Trp Pro Ser Leu Leu Arg His Arg Phe Leu Glu Glu Phe Ile Thr Pro 585 590 Pro Glu Phe Glu Glu Trp Lys Ser Ser Thr Pro Asn His Lys Lys Trp 595 600 Lys Val Lys Tyr Tyr Lys Gly Leu Gly Thr Ser Thr Ser Lys Glu Ala 615 Lys Glu Tyr Phe Ala Asp Met Lys Arg His Arg Ile Gln Phe Lys Tyr 630 635 Ser Gly Pro Glu Asp Asp Ala Ala Ile Ser Leu Ala Phe Ser Lys 645 650 Gln Ile Asp Asp Arg Lys Glu Trp Leu Thr Asn Phe Met Glu Asp Arg 660 665 Arg Gln Arg Lys Leu Leu Gly Leu Pro Glu Asp Tyr Leu Tyr Gly Gln 680 Thr Thr Thr Tyr Leu Thr Tyr Asn Asp Phe Ile Asn Lys Glu Leu Ile 695 700 Leu Phe Ser Asn Ser Asp Asn Glu Arg Ser Ile Pro Ser Met Val Asp 715 710 Gly Leu Lys Pro Gly Gln Arg Lys Val Leu Phe Thr Cys Phe Lys Arg 725 730 Asn Asp Lys Arg Glu Val Lys Val Ala Gln Leu Ala Gly Ser Val Ala 740 745 Glu Met Ser Ser Tyr His His Gly Glu Met Ser Leu Met Met Thr Ile 760 765 Ile Asn Leu Ala Gln Asn Phe Val Gly Ser Asn Asn Leu Asn Leu Leu 775 Gln Pro Ile Gly Gln Phe Gly Thr Arg Leu His Gly Gly Lys Asp Ser 790 795 Ala Ser Pro Arg Tyr Ile Phe Thr Met Leu Ser Ser Leu Ala Arg Leu 805 810 Leu Phe Pro Pro Lys Asp Asp His Thr Leu Lys Phe Leu Tyr Asp Asp 820 825 830 Asn Gln Arg Val Glu Pro Glu Trp Tyr Ile Pro Ile Ile Pro Met Val 840 845 Leu Ile Asn Gly Ala Glu Gly Ile Gly Thr Gly Trp Ser Cys Lys Ile 855 860 Pro Asn Phe Asp Val Arg Glu Ile Val Asn Asn Ile Arg Arg Leu Met 870 875 Asp Gly Glu Glu Pro Leu Pro Met Leu Pro Ser Tyr Lys Asn Phe Lys 890 885 Gly Thr Ile Glu Glu Leu Ala Pro Asn Gln Tyr Val Ile Ser Gly Glu 900 905 Val Ala Ile Leu Asn Ser Thr Thr Ile Glu Ile Ser Glu Leu Pro Val 920 Arg Thr Trp Thr Gln Thr Tyr Lys Glu Gln Val Leu Glu Pro Met Leu 935 Asn Gly Thr Glu Lys Thr Pro Pro Leu Ile Thr Asp Tyr Arg Glu Tyr 955

His Thr Asp Thr Thr Val Lys Phe Val Val Lys Met Thr Glu Glu Lys

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Leu	Lys 1010	_	Tyr	Asp	Thr	Val 1015		Asp	Ile	Leu	Arg 1020	_	Phe	Phe	Glu
Leu 1025		Leu	Lys	Tyr	Tyr 1030		Leu	Arg	Lys	Glu 1035		Leu	Leu	Gly	Met 1040
Leu	Gly	Ala	Glu	Ser 1045		Lys	Leu	Asn	Asn 1050		Ala	Arg	Phe	Ile 1055	
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Leu	Ile	Lys 1075		Leu	Ile	Gln	Arg 1080		Tyr	Asp	Ser	Asp 1085		Val	Lys
Ala	Trp 1090		Glu	Ala	Gln	Gln 1095		Val	Pro	Asp	Glu 1100		Glu	Asn	Glu
Glu 1105		Asp	Asn	Glu	Lys 1110		Thr	Glu	Lys	Ser 1115	_	Ser	Val	Thr	Asp 1120
Ser	Gly	Pro	Thr	Phe 1125		Tyr	Leu	Leu	Asp 1130		Pro	Leu	Trp	Tyr 1135	
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	1170)				1175	õ				1180)			
Glu 1185					1190)				119	5				1200
Lys				1205	5				1210)				1215	5
	_		1220)	_			122	5		Lys		1230)	
Lys		1235	5				1240)				1245	5		
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1265					1270)				1275					1280
Ala				1285	5				1290)				1295	5
			130) _				130	5		Phe	_	1310)	
Arg -		131	5				1320)				1325	5		
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1345	,				1350)	_			135				_	1360
				136	5				1370)	Gln	_		1375	5
			138)				138	5		Val		1390)	
		139	5				1400)			Glu	1405	5		
	1410)				1415	5	_			Ala 1420)			
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Thr Lys Arg Asp Pro Ala Leu Asn Ser Gly Val Ser Gln Lys Pro Asp 1445 1450 1455

Pro Ala Lys Thr Lys Asn Arg Arg Lys Arg Lys Pro Ser Thr Ser Asp 1460 1465 1470

Asp Ser Asp Ser Asn Phe Glu Lys Ile Val Ser Lys Ala Val Thr Ser 1475 1480 1485

Lys Lys Ser Lys Gly Glu Ser Asp Asp Phe His Met Asp Phe Asp Ser 1490 1495 1500

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<211> 284

<212> PRT

<213> Homo sapiens

<400> 224

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 Asp
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 Asp
 Arg
 Arg
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Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys

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Val Ile Glu Ser Arg Ala Gln Lys Asp Glu Glu Lys Met Glu Ile Gln
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Glu Ile Gln Leu Lys Glu Ala Lys His Ile Ala Glu Asp Ala Asp Arg
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                                        155
Lys Tyr Glu Glu Val Ala Arg Lys Leu Val Ile Ile Glu Ser Asp Leu
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                                    170
Glu Arg Ala Glu Glu Arg Ala Glu Leu Ser Glu Gly Lys Cys Ala Glu
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                                                    190
Leu Glu Glu Glu Leu Lys Thr Val Thr Asn Asn Leu Lys Ser Leu Glu
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Ala Gln Ala Glu Lys Tyr Ser Gln Lys Glu Asp Arg Tyr Glu Glu Glu
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Ile Lys Val Leu Ser Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu
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Phe Ala Glu Arg Ser Val Thr Lys Leu Glu Lys Ser Ile Asp Asp Leu
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Glu Asp Glu Leu Tyr Ala Gln Lys Leu Lys Tyr Lys Ala Ile Ser Glu
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Tyr Ser Asn Val Ile Phe Leu Glu Val Asp Val Asp Cys Gln Asp
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Val Ala Ser Glu Cys Glu Val Lys Cys Thr Pro Thr Phe Gln Phe Phe
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Leu Glu Ala Thr Ile Asn Glu Leu Val 100 105

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<211> 783

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<211> 179

<212> PRT

<213> Homo sapiens

<400> 228

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Gln Glu Pro

165

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gaacatgtcc ggtctaagac caaggttcct gtgcaggacc aggttctttt gctgggctcc 180
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Ile Lys Glu His Val Arg Ser Lys Thr Lys Val Pro Val Gln Asp Gln
                            40
Val Leu Leu Gly Ser Lys Ile Leu Lys Pro Arg Arg Ser Leu Ser
                        5.5
Ser Tyr Gly Ile Asp Lys Glu Lys Thr Ile His Leu Thr Leu Lys Val
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Val Lys Pro Ser Asp Glu Glu Leu Pro Leu Phe Leu Val Glu Ser Gly
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Asp Glu Ala Lys Arg His Leu Leu Gln Val Arg Arg Ser Ser Val
           100
                                105
                                                    110
Ala Gln Val Lys Ala Met Ile Glu Thr Lys Thr Gly Ile Ile Pro Glu
                            120
                                                125
Thr Gln Ile Val Thr Cys Asn Gly Lys Arg Leu Glu Asp Gly Lys Met
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Tyr Cys Ile Gly Gly
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Gly Pro Val Met Phe Arg Asp Val Ser Ile Asp Phe Ser Gln Glu Glu
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Trp Glu Cys Leu Asp Ala Asp Gln Met Asn Leu Tyr Lys Glu Val Met
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Leu Glu Asn Phe Ser Asn Leu Val Ser Val Gly Leu Ser Asn Ser Lys
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Pro Ala Val Ile Ser Leu Leu Glu Gln Gly Lys Glu Pro Trp Met Val
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Asp Arg Glu Leu Thr Arg Gly Leu Cys Ser Asp Leu Glu Ser Met Cys
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Ile Thr Arg Glu Asp Met Ser Thr Phe Ile Gln Pro Thr Phe Leu Ile
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Pro Pro Gln Lys Thr Met Ser Glu Glu Lys Pro Trp Glu Cys Lys Ile
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Cys Gly Lys Thr Phe Asn Gln Asn Ser Gln Phe Ile Gln His Gln Arq
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Lys Lys Pro Tyr Glu Cys Lys Glu Cys Gly Lys Ala Phe Ser Cys Ser
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Phe Thr Gln His Ser Arg Leu Ile Gln His Gln Arg Met His Thr Gly
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Glu Lys Pro Tyr Glu Cys Lys Gln Cys Gly Lys Ala Phe Asn Ser Ala
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Ser Thr Leu Thr Asn His His Arg Ile His Ala Gly Glu Lys Leu Tyr
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Glu Cys Glu Glu Cys Arg Lys Ala Phe Ile Gln Ser Ser Glu Leu Ile
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Gln His Gln Arg Ile His Thr Asp Glu Lys Pro Tyr Glu Cys Asn Glu
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                                            380
Cys Gly Lys Ala Phe Asn Lys Gly Ser Asn Leu Thr Arg His Gln Arg
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Pro Ser Trp Ser Phe Pro Ser Asn Leu Gly Thr Lys Thr Ala Asp Leu
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Lys Gly Ala Ser Glu Leu Pro Thr Pro Cys His Glu Cys Arg Glu Asp
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Asn Asp Gly Glu Gly His Ala Arg Pro Gln Ser Gly Met Lys Pro Leu
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Thr Glu Gly Met Arg Lys Asn Gly Thr Trp Leu Gln Ala Thr Ala Ala
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Thr Thr Arg Asp Cys Gly Val Asn Pro Glu Glu Ala Asp Ser Ala Phe
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<212> PRT

<213> Homo sapiens

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                           40
Lys Lys Ile Ile Glu Thr Lys Met Leu Met Gly Glu Val Met Arg Glu
                        55
Ala Ala Phe Ser Leu Ala Glu Ala Lys Phe Thr Ala Gly Asp Phe Ser
                    70
                                        75
Thr Thr Val Ile Gln Asn Val Asn Lys Ala Gln Val Lys Ile Arg Ala
                85
                                    90
Lys Lys Asp Asn Val Ala Gly Val Thr Leu Pro Val Phe Glu His Tyr
                                105
His Glu Gly Thr Asp Ser Tyr Glu Leu Thr Gly Leu Ala Arg Gly Gly
                            120
Glu Gln Leu Ala Lys Leu Lys Arg Asn Tyr Ala Lys Ala Val Glu Leu
                        135
Leu Val Glu Leu Ala Ser Leu Gln Thr Ser Phe Val Thr Leu Asp Glu
                    150
                                        155
Ala Ile Lys Ile Thr Asn Arg Arg Val Asn Ala Ile Glu His Val Ile
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                                    170
                                                        175
Ile Pro Arg Ile Glu Arg Thr Leu Ala Tyr Ile Ile Thr Glu Leu Asp
           180
                                185
                                                    190
Glu Arg Glu Arg Glu Glu Phe Tyr Arg Leu Lys Lys Ile Gln Glu Lys
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                                                205
Lys Lys Ile Leu Lys Glu Lys Ser Glu Lys Asp Leu Glu Gln Arg Arg
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<212> PRT

<213> Homo sapiens

Asp Val Asn Leu Pro 275

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